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THE PRINTING OF ROENTGEN NEGATIVES ON PAPER[1]

by

Arne Fraåtzell

The difficulty of transferring a roentgen negative to print without noticeable impairment is well-known. Almost all roentgen literature, as well as textbooks on roentgen diagnostics, witness to this difficulty. Often not even the most important details necessary for the interpretation of the picture come out with desirable clarity, and it is not rare to find reproductions where large, detailed parts of the roentgen film are represented of surfaces which are just black or white and completely without details. Naturally, such pictures have small value and can sometimes even make the expert reader doubt the interpretation which the author gives the pictures.

At the reproduction of a photographic negative or positive one begins as a rule with a paper print. As there are evidently no greater difficulties concerning the reproduction of a paper print of a roentgen film than a paper print of any other film, the difficulty which is entailed in transferring the original roentgen negative into print then depends almost entirely on certain special difficulties in making a paper print of a roentgen negative.

These difficulties are easy to understand if one remembers a number of facts concerning the technique of copying.

Thanks to the fact that they must be observed in reflected light, all pictures on printing paper have a relatively small density range. While the lightest surfaces of the paper picture only reflect 70—80 % of the light, the parts of maximum black reflect one or two percent. The density range of the paper picture can therefore, independently of the type of emulsion, rise only to a comparatively low figure. If, in the usual manner,

[1] Submitted for publication, Nov. 25, 1949.

From the Roentgen Department of the University Hospital in Uppsala, Sweden (Chief: Prof. HUGO LAURELL).

the density in reflected light is indicated by $D_r = \log \frac{I_i}{I_r}$, where I_i represents the intensity of incident light and I_r of reflected light, the highest value for D_r is about 1.6—1.7. This value is good for glossy paper. Matter paper can certainly show greater reflection in the lighter parts, but because the reflection in the shaded parts of this paper is proportionally greater than with glossy paper, the total density range of the matter paper therefore becomes smaller. The small density range of the copying-paper generally puts no hindrance in the way of a correct reproduction of a picture when copying *ordinary negatives*. Most negatives can certainly retain a rather high degree of density (up to c:a $D = 2$), but a majority of subjects (here we are not considering roentgen subjects) do not have such a great »tone range» that the entire density range of the negative needs to be made use of. In the cases where the density range of the negative more or less exceeds the greatest density range which a paper copy can have, one still can include the entire tone range of the negative within the scope of the limited density range of the print by copying the negative on a paper of soft gradation, which, thanks to the fact that it is less sensitive than »normal» and »hard» paper to variations in the intensity of the light, has a relatively greater printing range than the latter papers. Through this, however, the contrast between the different density tones is lessened, something which naturally must not be carried too far if the contrast from the very beginning is slight in certain parts of the picture and perhaps cannot be further reduced.

Very often the *roentgen negative* has a considerably greater density range than other photographic negatives. The special difficulties which often accompany the copying of a roentgen negative on paper will be mentioned later, but first a few words concerning why roentgen films and roentgen negatives have the abovementioned quality.

The one-layer glass plates, which were earlier used in roentgen photography, were exposed without the help of intensifying screens and pictures thus taken did not noticeably differ in respect to density from ordinary negatives. They were made, of course, as rich in silver as possible in order to obtain the greatest possible absorption of the roentgen rays in the light-sensitive layer, but an increase in the amount of silver halogen is mainly brought about by increasing the thickness of the emulsion layer, and this could only be increased moderately for reasons of development technique. It is for this reason that one very often finds, in the older roentgen literature, roentgen pictures which from the point of view of reproduction technique are of a considerably higher class than those we are accustomed to see in the roentgen literature of a later date. The relatively soft and harmonic roentgen negatives of that day were well suited for copying on paper, either directly or after re-

photographing. One avoided the difficulties of technical reproduction by appending the original prints of the pictures (see, for example, Fortschritte d. R-str. 1908, Ergänzungsband 16).

By introducing thin nitro or acetate cellulose film as a supporting base for the silver halogen in place of glass plates, it was possible to cover both sides of the supporting layer with silver halogen. This was not possible with the glass, for the thickness of the latter caused the silver layers to lie so far apart from one another that a troublesome parallactic error appeared both at the observing of the negative and its copying.

Through the doubling of the sensitive emulsion layer the d e n s i t y r a n g e of the photographic material was doubled (the straight-line portion of the characteristic curve became twice as long). With this one also could reach very high density values up to D = 4 (and in certain cases more), that is to say densities which let through only 1/10,000 of the light or even less.[1]

The double layer also brought about, as a matter of fact, an increase in the contrast. If the contrast between two adjacent surfaces in a picture is represented as the difference between their density grades, and if one assumes that the density within the first area = d and within the second area = 2 d, then d becomes 2 d, and 2 d becomes 4d at the doubling of the layers, that is to say the contrast is doubled. When read on a characteristic curve the double layer results in a doubling of the γ-value. ($\gamma = \mathrm{tg}\,\alpha$, where α represents the inclination angle, to the abscissa, of a tangent which is drawn through the turning point of the characteristic curve.)

There is yet another factor which has increased to a great extent the contrast of the roentgen negative, the *introduction of intensifying screens* in the roentgenography. The increase in the contrast here depends, among other things, on the different courses taken by the characteristic curve when photographing with roentgen rays and with visible light. In the former case the curve at first rises upwards (practically speaking) in a straight line from the lowest exposure values. In the latter case the curve shows an upward rising value only after the exposure has reached a certain value, »the threshold value», but when there is a further increase in the light the density increases at a relatively faster pace than it does when only roentgen light is being used. The latter curve has then a higher γ-value.

If one desires to get satisfactory pictures, on printing paper, from modern contrast-rich roentgen negatives, one must in general make use

[1] As is known, the density (= D) is defined as the logarithm of the opacity (quotient between the intensity of the incident and the transmitted light). According to this definition a layer of density grade 1 lets through 1/10 of the light, a layer of density grade 2, 1/100 of the light, and so on.

of special methods. Many methods have already been proposed and worked out during the years, and one distinguishes among them those, on the one hand, which concentrate on getting a good original negative at the actual roentgen photographing, and on the other hand, those which only build on special processes in the copying technique.

As the methods of the first-named group really fall outside the scope of this paper, I wish only to mention one or two which have now and then been used in our roentgen department. Above all I refer to photographing without intensifying screens, but also to the use of wood, metal and paraffin wedges or of thin waterfilled rubber bladders and similar aids which equalize the differences in thickness and roentgen denseness of the different parts of the photographed body. Even photographing of parts of the body which have been completely or partially submerged in water has been successfully experimented with, chiefly in connection with the study of soft parts. Furthermore, telephotography with hard radiation and a simultaneously increased distance between object and film has been used. (See the writings of LAURELL in the bibliography.) Several methods concerning the equalization of exposure which are mentioned in roentgen literature are worthy of notice, but they do not appear to have been put to any practical use. To this category belong, for example, the use of gradated metal filters; the simultaneous exposure of two films lying in the same plate-holder, of which only one touches an intensifying screen; and the introduction of gradated yellow filters between the film and the intensifying screen.

It is easy to see that for practical and economic reasons such methods are often avoided in routine work and are therefore mainly used only in those cases when one knowns beforehand that the roentgen pictures are going to be reproduced. In most cases the question of reproduction first occurs some time after the picture has been taken, and as it is then most often too late to re-take it, it is necessary to resort to special printing methods in order to get satisfactory prints.

Direct contact-printing is, of course, the simplest method of printing roentgen film on paper. For reasons already given, however, only a small percentage of modern roentgen films can be successfully printed in their entirety in this manner. One can, nevertheless, obtain useable paper prints from a considerably larger percentage of roentgen films if one first photographs a roentgen negative on an ordinary photographic plate or film and then prints it on paper, either by contact or projection printing. In the latter case one can get a considerably larger printing range than with direct contact printing, provided that one does the re-photograping on a film with a relatively soft gradation and provided also that at the development of this film one sees to it that it does not have so great a density range that it cannot be printed on paper in its

entirety with all its details. The latter is brought about most simply by short time developing or some other form of »surface developing». One must not forget, in this case, to over-expose the diapositive a little and on the whole to expose it with regard to the roentgen film's denser parts, in order, obviously, not to risk their being under-exposed or their disappearing entirely from the diapositive.

In many, indeed in most cases one does not obtain satisfactory paper prints through this indirect printing process either. Very often the softest photographic plate or film does not have a »printing range» sufficient to reproduce the sometimes very large density range of the roentgen negative; should this be the case, the diapositive in its turn will have too great a density range to permit its being printed on paper in its entirety.

If a roentgen negative is divided up into so many parts and in such a manner that each part is characterized by a relatively equal density, one will discover that all the parts can usually be printed on the same kind of paper, even if the paper is relatively hard. Every part of the negative must obviously be illuminated in proportion to its density. *Consequently it ought to be possible to print the roentgen film in its entirety, either directly or by re-photographing, if one when copying could illuminate the different parts of the film in proportion to the degree of their density.*

This principle concerning the printing of ordinary, unevenly exposed negatives has been known and employed by both professional and amateur photographers for many years. If one wishes, for example, to make a print of a negative, part of which is somewhat under-exposed and part somewhat over-exposed, with the dividing line between the thinner and denser parts comparatively sharp, one can, despite the uneven exposure, print it on relatively hard paper by cutting off the light from the thinner part of the negative so that both parts receive light in proportion to their density. This can be done either with the hand or in some other way during a part of the printing process. One must naturally see to it that the contour of the shadow is not produced on the print, which can be avoided by holding the shading agent a short distance from the negative, whereby its contour is less sharp, or preferably by also keeping it in motion during the exposure. As is well-known, such a shading procedure can often be employed with success at the printing of roentgen negatives. (In this way the author has printed most of the pictures in HULTÉN's paper: Cholangiographie während der Operation.) The method demands, however, quite a bit of practice since it is often very difficult to judge the difference in density in the different parts of the film.

Unfortunately, few roentgen negatives have such a division of density that one can, with such simple methods, bring about a fairly exact lighting-differentiation.

By experimenting with different shading methods, one got the idea

quite early that the best way to illuminate every part of the roentgen negative in proportion to its density would be to shade it, during the printing process, with its own contact-diapositive. This, of course, must have a somewhat smaller density range than the negative so that one does not produce a total equalization of the picture. About 1929 LAURELL tried to print contrast-rich roentgen negatives according to such a method. (This method was not published.) He succeeded in getting harmonious prints, but he also found out that it is practically impossible to get the two pictures — the negative and the positive — to tally exactly. If the pictures are only a fraction of a millimeter off center, the prints almost always have a relief appearance, a sort of false stereoscopic effect. Even if this method is quite attractive, one can nevertheless complain that it causes much too great an equalization of the picture's finer details. It is true that the details in such prints usually appear quite clear, but this depends on the displacement referred to above; if this could be completely done away with, one would quite naturally find that the contrast of the details has been equalized in about the same proportion as the other differences in density of the picture. This would mean that the relatively contrast-poor details which perhaps appear in several places in the negative do not come out with satisfactory clarity in the print.

In 1930, however, SPIEGLER and JURIS described a new printing method which was based on the old idea of shading the roentgen negative during the printing process with a diapositive of the same. But this was, so far, an improvement of the earlier method inasmuch as the diapositive was not a contact diapositive; instead the photographic plate, at the making of the diapositive, was placed at a centimeter's distance from it. The advantages of this method were the following: »The diapositive filter» (the term used by SPIEGLER and JURIS for the shading diapositive) became blurred and contained practically no details because at the reproduction it was not in contact with the negative. The contrast equalization which was the result of the final printing did not, therefore, affect the details. Besides, what was almost equally important, a minimal dislocation between the negative and the diapositive, which at LAURELL's experiments gave the picture a peculiar quality, could not bring forth the same unfavourable effect thanks to the blurred state of the diapositive. The publication in question contains a great many excellent roentgen reproductions, proving the great merits of the method, and one is surprised in the beginning that it has not become more widely known and used. In practice the method has its disadvantages, which may explain why one is disinclined to use it more generally. In the first place it is rather expensive to print at least the larger sizes when using this method. If, for example, one wishes to print a film, size 30×40 centimeters the theoretically smallest material expenditure is one diapositive

filter (roentgen film or ordinary glass plate), size 30 × 40 centimeters, and a printing paper of the same size. If one remembers, also, that the nature of the method very often requires the printing process in question to be repeated several times in order to get a satisfactory result, one understands that the costs for a single print easily rise to large sums. Besides one must have specially constructed printing frames for every picture size. If one wishes to print a detail of a picture, one must first print the whole picture, unless one wants to cut down the negative to a somewhat smaller size for which one has a printing frame. Finally it should be pointed out that the final paper print always appears in the form of a positive picture, as long as one does not wish to go to the expense of another plate or film of the same size as the roentgen film to be used as an intermediary toward a negative print.

ROBINSOHN, who in two works (1930 and 1931) treated quite thoroughly the question of the best method of copying a roentgen negative on paper, proposed entirely different methods than earlier or contemporary authors. In the first place, he went in for both a »fractional» illumination and a »fractional» development during the printing process. The fractional illumination implied that during the printing process the different parts of the roentgen negative were, with the aid of special small lights, illuminated in proportion to their density, that is to say, an illumination-differentiation which is entirely based on a subjective estimate of the difference in density within the different parts of the negative. The fractional development of the print implied that after a considerably shortened development of the whole picture, the different parts were developed individually with the help of a brush or a piece of cotton. ROBINSOHN considered his method superior to that of SPIEGLER and JURIS despite the purely subjective factors it depends on.

For the present the author does not wish to take a position as to which of the two above-metioned methods is to be considered the simplest and most dependable, but to judge from the literature in this field, neither of these two printing methods nor any later ones have definitely solved the problem concerning the printing on paper of the modern roentgen film. In the Swedish »Fotografisk Handbok», printed in 1942, K. LINDBLOM has written one chapter concerning »the printing of roentgen pictures», which doe not take exception to this opinion.

My Own Method

Without knowing the method of SPIEGLER and JURIS, the author invented in the autumn of 1941 a shading method for the printing of roentgen film which in principle somewhat resembled theirs, but which was quite different in its important details. The author described the method in a

lecture before the *Swedish Association for Medical Radiology* in the autumn of 1944. I also made a blurred diapositive, intended as a shading agent but not the same size as the original picture; it was much smaller, 24 by 36 mm. This little diapositive was enlarged afterwards to the size of the original picture with the help of a small-print projector. With a special contrivance one got the projected (blurred) picture to cover the original picture exactly and the picture thus shaded was photographed with a camera usually in a 9 × 12 cm. size, from the side opposite the projector. One thus obtained a diapositive with levelled contrasts, from which one could make contact prints in the usual manner; these prints were most often satisfactory, even if it was sometimes difficult to avoid entirely a »pseudo-relief».

This method had, above all, one advantage over the method of SPIEGLER and JURIS: the costs of the photographic material were brought down to a minimum. Nevertheless the cost of making the print remained quite high, a fact which depended on the long time taken by the entire printing process: for on the one hand the shading diapositive had to be dried before being used, inasmuch as it could not withstand the heat from the small-print projector when it was wet; and on the other hand the exposure-time (at the photographing of the shaded original negative) was very long, often a half hour or more, an example, among other things, of »the Schwarzschild effect». Other disadvantages of the method were the very bulky apparatus, the difficulties in sufficiently reducing great contrasts in the negatives, and the difficulty in the main of varying the degree of the contrast-levelling in a desirable way, a disadvantage which the author's method had in common with the method of SPIEGLER and JURIS.

During the last year the author has modified and improved his method so that the above-mentioned disadvantages have been more or less eliminated. Inasmuch as the original and the modified methods differ considerably from one another and as the latter is the most practical and also gives the best results, the latter only will be described in detail.

Apparatus

The most important part of the apparatus used by the author in recent times is an instrument for the enlarging of a 6 × 9 cm. negative. (Fig. 1.) Under its objective and on the base (B) of the apparatus are placed two wooden blocks (C) supporting a frosted glass plate (P), 30 × 35 cm. in size. The frosted glass plate lies 20 cm. above the base and is parallel with it. Underneath the plate, on the base itself, are placed two light globes (G). The distance between the globes and the glass plate (and the distance between the globes themselves) is so arranged, that

when the globes are lit, an even illumination is obtained on the glass plate. At the place where the negative-holder of the enlarging apparatus is situated there is placed a metal frame (F), the construction and purpose of which will be described in more detail below.

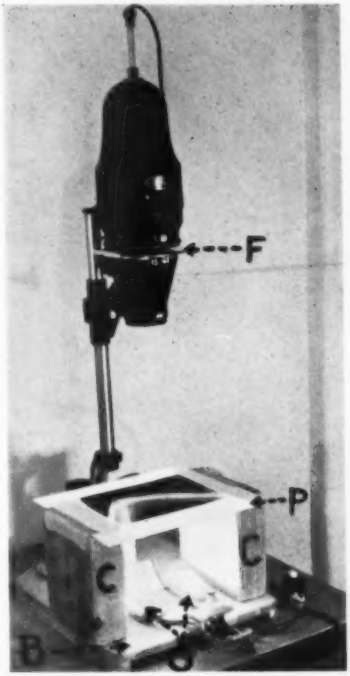

Fig. 1. Apparatus.

The Printing

One first focuses the enlarging apparatus in relation to the subjacent plate of frosted glass in such a way that one obtains so large a projection distance that a 6×9 cm. picture, projected through the enlarging apparatus on the frosted glass plate, is reproduced in a somewhat larger size than the roentgen negative which one intends to print. Furthermore, the objective of the apparatus must be so adjusted that the picture projected on the frosted glass plate obtains a certain, most often relatively high degree of blurredness. This is quite simply done by moving the objective upwards or downwards from that place where the picture is sharp.

When these adjustments have been made, the roentgen negative is placed on the frosted glass plate and is fastened along one side of it with a narrow strip of leucoplast. In order that the film will lie flat it is covered by a sheet of ordinarily transparent, flat, relatively thick glass. One intends as a first step to produce a blurred, reduced diapositive of the original negative, using the enlarging apparatus as a camera. Therefore a glass plate, size 9×12 cm., is inserted in the enlarging apparatus, with the emulsion side downward, at the position of the negative holder. One chooses preferably a relatively contrast-rich plate, for example a reproduction plate, and obviously at its insertion only a harmless dark-room light may be used.

It must now be remarked that the plate must be put in the enlarging apparatus in such a way that after its exposure and withdrawal for development it can be put back, if possible, in exactly the same place as before. In order to make this possible a metal frame, specially made for the purpose, has been placed in the position of the negative holder; this

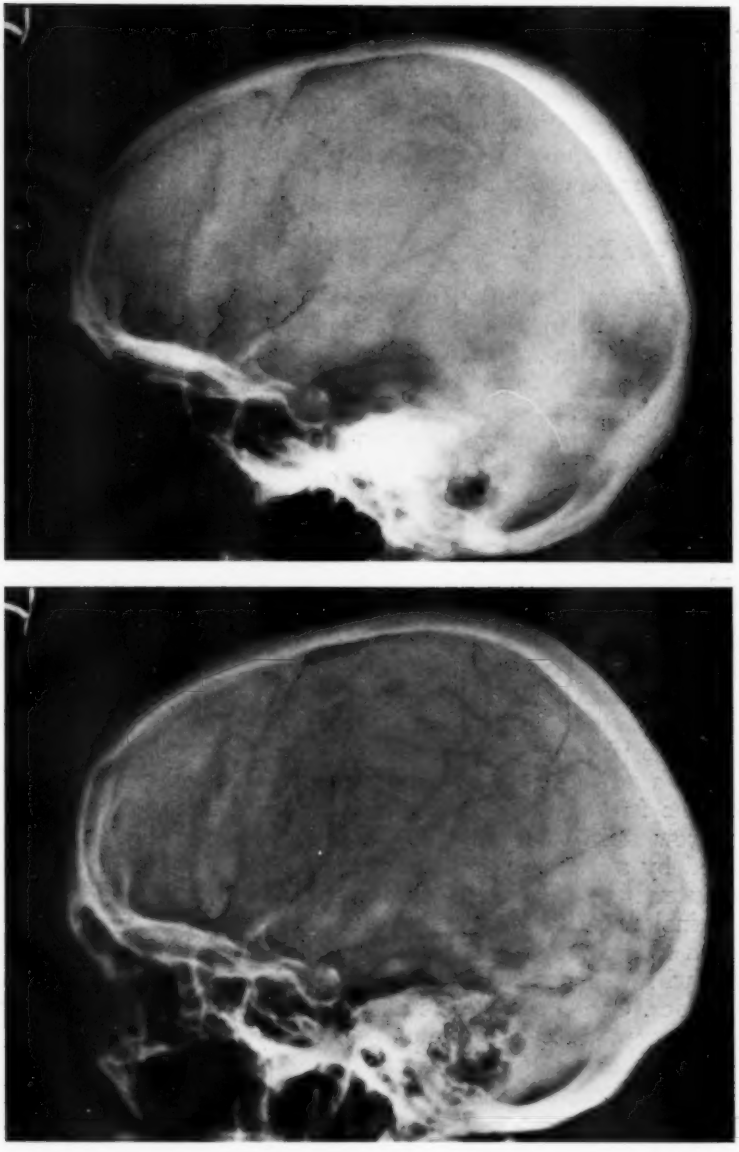

Fig. 2 a

Fig. 2 b

Fig. 2. Ordinary skull picture.
a) Ordinary copy. b) Tone separation copy.

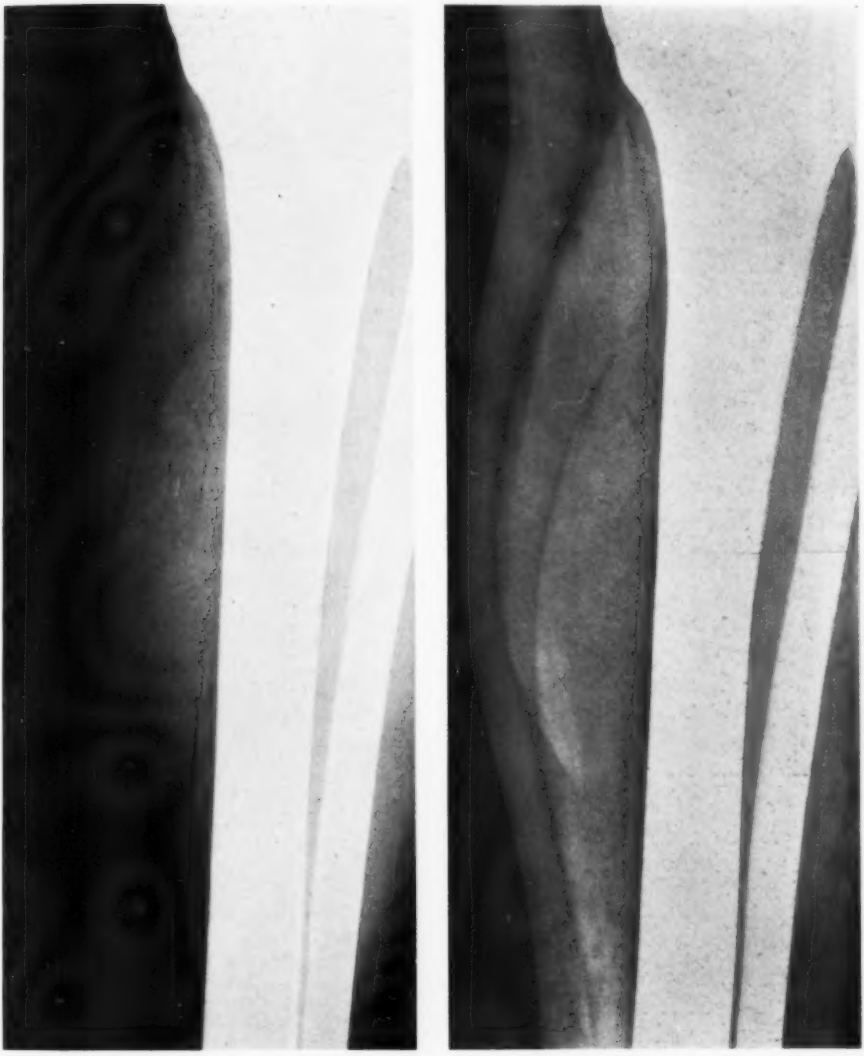

Fig. 3 a. Fig. 3 b.

Fig. 3. Soft tissue picture of the lower leg. Normal case ♀ 25 years of age.
a) Ordinary copy. b) Tone separation copy.

Fig. 4. Soft tissue picture of the lower leg by dystrophia musculorum progr. Ordinary copy.

Fig. 5. The same case as on fig. 4; tone separation copy.

Fig. 6 a.

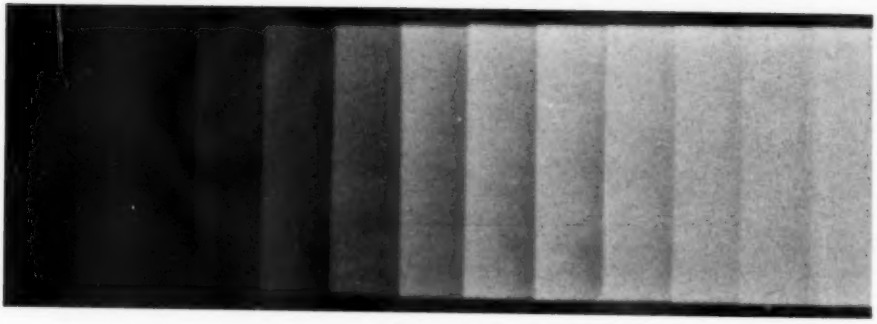

Fig. 6 b.

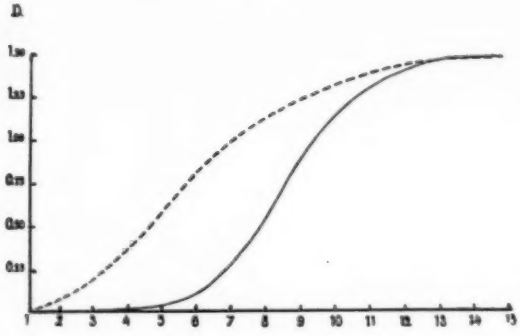

Fig. 6 c.

Fig. 6. Roentgen picture of an aluminium step wedge.

a) Ordinary copy.
b) Tone separation copy.
c) The continuous curve represents the density in the different steps of the diapositive to the ordinary copy above. The broken curve represents the diapositive of the tone separation copy.

Fig. 7 a.

Fig. 7 b.

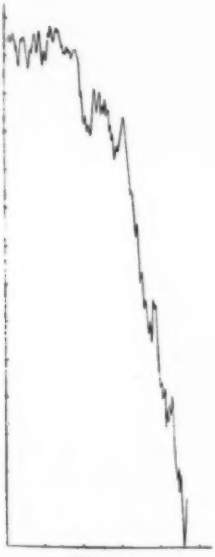

Fig. 7 c.

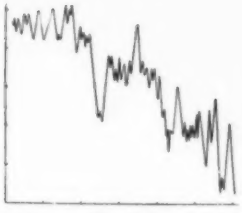

Fig. 7 d.

Fig. 7. Soft tissue picture of the musculus gastrocnemius region. Normal case ♀ 65 years of age.

a) Ordinary copy.

b) Tone separation copy.

The curves beneath the pictures are microdensitometer curves of the diapositives to the pictures. They are registrated on the lines, drawn on the copies.

Fig. 8 a. Fig. 8 b.

Fig. 8. Panniculus adiposus on the inside of the thigh. 90 minutes after subcutaneous injection of 12 cc. physiological NaCl solution.
a) Ordinary copy. b) Tone separation copy.

frame has a rectangular opening, size 6 × 9 cm., and a short, vertical partition which, when the frame is inserted in the enlarging apparatus, lies at right angles to the posterior vertical partition in the opening for the negative holder. By inserting the plate so that two of its edges rest against the above-mentioned partitions of the frame and the enlarging apparatus, it is easy, after the withdrawal of the plate, to place it again

in the same place as before, provided that the frame is well fastened to the apparatus.

The exposing of the above plate occurs when the lights on the base of the apparatus are lit. During this process the plate should be covered with black paper as a protection against the diffused light coming in from the sides. (In the author's experiments the exposure time has generally been from several seconds to half a minute. This has, of course, depended both on the density of the original negative and on the strength of the lights.) Immediately after the exposure the plate is developed, fixed, and washed a couple of minutes, after which it is put back in a wet condition in the same place as before, this time, however, without the protective paper. Now if one turns on the light of the enlarging apparatus, *the roentgen picture lying on the frosted glass plate will be shaded in such a way that every part of the film will be illuminated in proportion to its density*. Thanks to the fact that the shading diapositive is blurred, the details of the picture will be scarcely or not at all affected by the shading. For a fuller description of the results of shading, see below.

The printing of the original negative is now accomplished by inserting, in a suitable dark-room light, an unexposed roentgen film of the size of the negative between the negative and the frosted glass plate. A sheet of glass is placed, as before, on the roentgen negative; this ensures that the two films will come in direct contact with one another. Thanks to the pronounced shading, the exposure can take several minutes (during which time the lights on the base of the apparatus should, of course, be turned off). After the exposure the film is developed, and one obtains a diapositive which is harmonious from a photographic point of view and suitable for printing on paper either in full or reduced scale.

On pages 10—16 can be seen pictures printed with the help of the above described contrast-equalization method. For the sake of comparison the same pictures are shown, printed without the use of a shading diapositive but otherwise in the same way. These latter prints may be said to represent the best results one can expect to reach when printing pictures by ordinary methods. This method was used for the first time in HOLMGREN's work »Flüssiges Fett im Kniegelenk nach Trauma» 1942. For other examples of pictures printed with the help of the author's method, see HOLMGREN's inaugural dissertation (Acta radiologica suppl. LXI, all roentgen pictures except the reproductions of roentgen moving pictures), SKARBY's inaugural dissertation (Acta radiologica suppl. LXII, Abb. 14—22 inclusive), and the author's article: »Röntgenologische Weichteilsstudien von Cutis und Subcutis . . .» (Acta radiologica Vol. XXV, 1944, Fig. 3—6 inclusive). The pictures published by SKARBY and by HOLMGREN are, however, not compared with pictures printed

in the ordinary way, which means that without seeing the original negative one cannot get an idea of the density range of the latter pictures or of the importance of contrast equalization as far as the quality of the reproduced picture is concerned. Most of the reproductions are of the soft tissues of the body. This depends, among other tings, on the fact that one of the reasons why this method came into existence was that the author, when trying to reproduce some pictures of soft tissues, found that this could not be accomplished without special aids. When afterwards a useable printing method was gradually developed, it was tested primarily with pictures of soft tissues; and these pictures, with their great density range and often very contrast-poor details, are among the best examples of roentgen negatives which necessarily demand special copying methods in order to be reproduced in print.

Printing methods which are based on the same principles as the one described by the author are generally referred to in the literature on the subject as »*tone separation methods*». Several such methods have been earlier described in the literature, but I am of the opinion that of these only the method of SPIEGLER and JURIS is practical in the printing of roentgen negatives. The expression *tone separation* means that during the printing process one does not effect a contrast equalization which is distributed equally within the density scale of the picture. Such an equalization, as far as most roentgen negatives are concerned, would mean a certain impairment, in that many details in the picture would not have sufficient contrast. In the above described shading process the contrasts are retained or increased both within the picture's lightest and darkest parts, while on the other hand the contrasts within the intermediate tones are considerably subdued. This is desirable for two reasons. First, the contrast-rich roentgen negatives are usually poor in intermediate tones, and second, the often very great contrast in these tones has a strong tendency to be further accentuated during the printing process because of the S-like density curve of the printing material. One can, therefore, considerably subdue the contrast in the intermediate tones without its being necessary to distort the picture or even give it a foreign character. A certain unfamiliar impression in comparison with the original can, however, be received in copies of such roentgen negatives, the density range of which is very great, and where the contrast equalization must therefore be considerably extended. In such cases one can obtain copies in which all the details of the original negative appear with satisfactory contrast, but in which one does not get the most characteristic quality of the negative, the great density differentiation within the intermediate tones. It must, however, be considered much more important to make a print which is the equivalent of the original diagnostically than, at any price, to make it photographically identical with it. This

latter is quite impossible in any event when paper copies of roentgen negatives are concerned.

To illustrate more completely the significance of the above described tone-separation process, prints are shown, on Fig. 6, of a roentgen picture of an aluminium step wedge produced both by ordinary methods and by tone separation. On the same side one can see two curves representing the density of each step in the diapositives of the step wedge copies. The importance and significance of tone separation are further illustrated on Fig. 7. It shows microphotometer curves, recorded according to the lines drawn in figures above. To the left the curve of a non-tone-separated diapositive of the aforementioned negative. To the right the microphotometer curve of the tone-separated diapositive of the same area. From these curves one can read directly that the density range at the tone separation is considerably decreased, while the contrast in the details is retained.

It is not within the scope of this paper to describe the printing method in detail with a complete account of, for example, the degree of blurredness one ought to give the shading diapositive in different cases, how this is accomplished by a focusing of the enlarger's objective, and what a certain amount of blurredness in combination with development to a certain gradation implies so far as the degree of contrast equalization is concerned, and so forth. Here it will only be added that the author's method, despite its theoretical simplicity, is quite complicated in practice, and that it entails a good deal of work, during which a subjective judgement is a determining factor in obtaining results. For the time being, therefore, this method will probably be used by persons who are not only well trained in the theory and practice of the usual printing techniques, but who have also acquired sufficient practical experience in this special method. Certainly, however, the method can gradually be considerably simplified.

With this paper the author has hoped to show that with the help of the above method one can really bring about very good prints even from those roentgen negatives which do not give satisfactory prints with the help of the usual printing methods. The author, of course, does not mean that such a complicated and expensive method is to be used if ordinary printing methods are sufficient to give a satisfactory result. Nor must one, whether one uses this method or not, forget the general and important rules for the reproduction of pictures in print, *i. e.* the importance of using good printing paper and of reproducing the picture in a sufficiently large size. One ought to remember that even if the original print is very good, the reproduction can be quite unsatisfactory if the original print is reduced so much that important details disappear.

In conclusion I should like to express my warmest thanks to Mr. Bernt Eriksson, photographer of Idrottsmagasinet in Uppsala, who with never failing interest assisted me with the working out of this method. His photographic knowledge and his wide experience in making prints have been of great help to me. On my instructions he has made most of the prints which are here reproduced or to which reference is made.

SUMMARY

The roentgen negative of to-day is difficult to transfer to print because of its very great density range. The author describes a special »tone separation method» for copying roentgen negatives on paper. The most important part of the apparatus is an instrument for the enlarging of 6 × 9 cm. negatives. An unsharp diapositive in diminished scale is first produced when the enlarging apparatus is used as a camera. At the definite copying this diapositive is projected on the roentgen negative whereby the different parts of the latter are illuminated in proportion to their density. This is why the contrasts are equalized a good deal at copying. Thanks to the fact that the shading diapositive is blurred, the details will not be affected.

The method has perhaps its greatest use in copying soft tissue pictures.

ZUSAMMENFASSUNG

Unsere heutigen Röntgennegative sind wegen ihres hohen Schwärzungsumfanges schwer in Druck wiederzugeben. Verf. beschreibt eine besondere Tontrennungsverfahren zum Kopieren von Röntgennegativen auf Papier. Der wichtigste Teil des Apparats ist ein Instrument zur Vergrösserung von Negativen von 6 × 9 cm. Zuerst wird durch Verwendung des Vergrösserungsapparats als Aufnahmeapparat ein unscharfes, verkleinertes Positiv hergestellt. Bei der endgültigen Kopierung wird dieses Positiv auf das Röntgennegativ projiziert, wobei die verschiedenen Partien dieses letzteren im Verhältnis zu ihrer Schwärzung beleuchtet werden. Hierdurch werden beim Kopieren die Kontraste ziemlich stark ausgeglichen. Weil das schattengebende Positiv unscharf ist, werden die Einzelheiten nicht betroffen.

Die Methode findet vielleicht ihre grösste Verwendung beim Kopieren von Weichteilsaufnahmen.

RÉSUMÉ

Le négatif d'un film Roentgen actuel est difficile à reproduire par l'impression à cause de ses très grandes différences de densité. L'auteur décrit une méthode spéciale de »séparation des tons» pour tirer sur papier les négatifs radiographiques. La partie la plus importante de l'appareil est constitutée par un instrument pour l'agrandissement de négatifs de 6 × 9 cm. On établit d'abord un diapositif flou de dimensions réduites en se servant de l'appareil agrandisseur en guise de chambre noire. Lors du tirage définitif de l'épreuve, l'image de ce diapositif est projetée sur le film Roentgen négatif, ce qui éclaire les diverses parties de ce dernier proportionellement à leur densité. Ainsi les contrastes sont égalisés dans une large mesure pendant le tirage de l'épreuve. Et grâce au fait que le diapositif jouant le rôle d'écran est flou la finesse des détails n'en souffre pas.

La méthode trouve peut-être son meilleur emploi dans la reproduction des images des parties molles.

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FROM THE MEDICAL CLINIC (DIRECTOR: PROFESSOR ERIK ASK-UPMARK) AND THE ROENTGEN DEPARTMENT (DIRECTOR: PROFESSOR HUGO LAURELL) OF THE UNIVERSITY HOSPITAL OF UPSALA, SWEDEN.

ON THE PATHOPHYSIOLOGY OF A PECULIAR SYNDROME OF ACUTE ABDOMINAL DISTENSION[1]

by

Erik Ask-Upmark and *Arne Frantzell*

It is a well known phenomenon that several individuals, particularly perhaps about their middle age, may experience some increase of their abdominal circumference after meals necessitating the unbuttoning of their garments. Occasionally, this increase may occur also in young individuals and be quite considerable. Thus, in a previous paper, one of us (A.-U.) has described this phenomenon in young girls: it was confined to the week preceding the menstruation, it had nothing to do with the kind of food consumed and it might be of quite outstanding dimensions, even so as to suggest a pregnancy in the last months (thus, in one girl, aged 19, the waist circumference increased from 60 to 96 cm.). As a rule the abdominal distension hence to be noted returned to normal levels within one hour after the meal. We were not able to furnish any definite explanation of this peculiar phenomenon, although it was felt that it had to do with some sort of reflex mechanism. Aerophagy and acute ventricular dilatation were excluded by roentgen examination and the question was raised whether not the vascular conditions of the liver had something to do with it. It was, however, impossible to register any definite enlargement of the liver and it should be observed that this investigation was being performed in conjunction with the department of HANS HELLMER, the famous radiologist in Lund, whose untimely death we regret and who had taken a special interest in the roentgenologic reproduction of the liver.

We have recently had the opportunity to observe a case apt, as we believe, to throw some light on the patho-physiology of this peculiar syndrome.

[1] Submitted for publication Dec. 12, 1949.

Case Report

edical Clinic 559/1949. Engineer, aged 38. Observed in the clinic Febr. 23rd—March 12th and May 23rd—May 25th.

Family history: His father died, aged 69, from cancer of his stomach, his mother, aged 49, from meningitis. The patient ranks nr 8 out of 9 siblings. One sister died aged 45 from »cancer of the liver», one sister, aged 21, from septichaemia, one sister, aged 12, from diphteria and one as a newborn. The remaining 4 siblings are all alive and healthy. His wife died 2 years ago (accident). He has three children. One son, now aged 11, had at the age of 4 the same symptoms as his father now applies for, they appeared in connection with a bilateral pneumonia and subsided after some time. When aged 7 this son had another similar period, the attacks appearing mostly in the evenings and as often as 3 or 4 days a week. A daughter, now aged 6, had the same peculiar syndrome for a fortnight one year ago.

Social history: The patient is an engineer connected with one of our large wood-refining companies in the North of Sweden. He occupies a topranking position and has made several important technical inventions, registered all over the world. He enjoys his work and his children and is on the whole entirely satisfied with his achievements in life. His household is being managed by a female householder, obviously a quite able person. His daily routine is as follows: arising at 7.45 he has a breakfast of porridge and eggs, between 9 and 13.30 he is busy at the office and has afterwards luncheon at home (the main meal of the day). He is back at the office at 14.30, working until about 17, and has then a light dinner at home. Later in the evening he takes a cup of tea and goes to bed at 23 o'clock. He smokes 3—4 cigarettes a day and has very moderate habits regarding had liquors (consumption about 1 pint a month). When aged 20, he did not do his ordinary military service because of trouble from his stomach (vide infra); in 1940, however, he was accepted for military service and did such service without any difficulties in the year 1943.

Medical history: As a child he had morbilli, in 1945 he was operated upon for a left-sided spermatocoele and in 1946 for appendicitis without any complications. He was accepted for insurance on ordinary terms in 1947. Ever since the age of about 20, however, he has had difficulties with his stomach along the line of the ulcer disease: pains and a feeling of suction in the epigastrial region, when hungry, comforted by food. Repeated roentgen examinations have failed to disclose any ulcer but with regard to his gastric juice »too much acid» has been registered repeatedly. Since 1944 these troubles have practically ceased to disturb him. Otherwise his previous history is blank, only should it be remarked that ever since childhood, he has had a certain liability to get diplopia when tired, for instance in the evening.

His present illness started Jan. 1948 with abdominal pains, appearing after meals and especially located below the right costal arch. The pains did not irradiate towards the back. At the same time he had persistent vomiting $^1/_2$—1 hour after the meal. He was admitted to a municipal hospital of high standard where a thorough examination (including such details as cholecystography and urography) failed to disclose anything abnormal. He returned home but forthwith he has been hampered by abdominal troubles of a quite peculiar character: he has no symptoms in the morning after the breakfast, occasionally some slight symptoms after luncheon but otherwise he is as a rule entirely up to his limit until dinner. In connection with his dinner the volume of his abdomen increases quite considerably the circumference exceeding the normal by some 8—10 cm. This phenomenon might be induced by his consumption of anything, for instance coffee, hot or cold water, milk, protein, sulfa-preparations etc. The only things that could be taken without provoking this abdominal distension were water at 37 C° or milk of the

same temperature. He had to unbutton his garments and lay down, the uncomfortable distension hence disappearing in one or a few hours. In Sept. 1948 he was examined in the same hospital again; nothing positively abnormal was to be elicited (roentgen examination of the stomach and of the colon, cholecystography, urography, fractionated test meal etc. were all normal and there were no clues indicating any adhesions from his appendectomy). Nov. 1948 he was again observed in the same hospital: it was impossible to register any aerophagy but about half a minute after his taking, for instance, a cup of coffee the abdomen was distended by 10 cm: it was easy to observe the contours of the ventricle since he had a certain degree of diastasis between his mm. recti abdominis. He was roentgen examined before and during a provoked attack and there was a certain amount of fluid and gas in the stomach and, to a less pronounced degree, in the colon. His weight has remained constant (78 kg.) and his general condition was good. The bowels were regular, no constipation being present.

Physical examination: On admission Febr. 23rd the general condition of the patient was very good. His weight was 78 kg., temperature normal, pulse rate 70, sedimentation rate 2 mm/1 hour and blood pressure 120/80. Mentally, the patient was well above average with regard to intelligence and he was very quiet, cooperative and objective with regard to his symptoms. His eyes had a certain glittering appearance, as frequently met with in individuals disposed to peptic ulcer. Physical examination of oral cavity, heart, lungs, reflexes and eyegrounds revealed entirely normal conditions. The abdomen was normal as well, only was there to be noted a certain diastasis between the musculi recti abdominis in the cranial part of linea alba. Palpation per rectum revealed normal conditions. A detailed neurological examination, including ophthalmology and otiatrics did not render anything abnormal (the possibility of hypothalamic involvement entailed these investigations). He was able to provoke an attack of considerable abdominal distension (difference of circumference some 10 cm.) in two ways: on the one hand by eating or drinking, particularly in the afternoon and in the evening, on the other hand on an empty stomach by pressing the tip of his finger towards the abdominal wall immediately below the processus ensiformis of the sternal bone: the pressure was thus exerted in the very midline and in dorsal direction and ought to be rather pronounced. This phenomenon could be reproduced by the examiner as well. Occasionally, the attacks were connected with hypersalivation.

Laboratory records: The urine was normal in every regard (amount, specific gravity, absence of albumen and sugar, occasionally solitary white blood cells in the microscope). The blood was repeatedly examined with regard to the sedimentation rate, which always was normal (2 or 3 mm/1 hour), the blood morphology was normal as well (hemoglobin 90 %, red cells 4.4 millions, white cells 4,300, differential count: neutrophiles 53 %, eosinophiles 4.4 %, lymphocytes 40 %, monocytes 2.5 %). The non-protein nitrogen was 31 mg%. Wassermann, Meinicke, Kahn negative. The liver was examined by the following tests:

Bilirubin: 0.43 mg%, no direct reaction; Takata: negative; Alk. phosphatase: 4.8 units; Thymol turbidity: 1.1 units; Hanger: +++; Weltman: 7.5; Citric acid: 15; Hippuric acid test (Quick): 1.1 gm. benzoic acid excreted in 4 hours; Galactose tolerance test: a) ad modum Bauer (40 gm. given per os): 2 Gm. excreted; b) ad modum Malmros-Silver-Swaetichin (78.5 gm. given per os); March 3rd: Blood sugar maximum 208 mg%, urinary excretion 7.6 gm. March 7th: Blood sugar maximum 268 mg%, urinary excretion 8.7 gm.

It may, hence, be said that with the exception of the galactose tolerance test, performed in the refined way devised by Malmros-Silver-Swaetichin, all tests were essentially normal. With regard to the galactose tolerance test it was positively pathological: even if performed along the lines indicated by Swaetichin and co-workers the excretion within

4 hours is not allowed to exceed 3 gm. and the maximal level of the blood sugar should never exceed 180 mg%. This is another illustration of how unreliable the Bauer test really is, although it seems safe to assume that had the Bauer test been performed repeatedly it should, in this case, have become positive once in a while.

Roentgen examination: The skull and sella turcica were normal. Repeated roentgen examinations of the stomach had already failed to disclose anything abnormal. In order to approach the pathophysiology of the peculiar syndrome in question a detailed analysis was performed by Dr. FRANTZELL, whose report runs as follows.

Febr. 26th 1949. The patient was firstly examined on some different occasions in order to find out whether any aerophagy was present. It turned out, however, that the stomach as well as the intestines rather contained strikingly small amounts of gas and that the patient did not swallow any air neither in connection with food nor in between.

The patient presents a certain diastasis of the abdominal recti-muscles and when examined in lateral projection both the stomach, the duodenum and parts of colon were situated very much ventrally. It was quite obvious that the increased volume of the abdomen at least partially was due to the pushing forwards of the abdominal viscera in the diastatic region just mentioned. In erect posture a lowering of the diaphragm was to be observed in connection with the consumption of contrast or food. He was now examined in the early morning on an empty stomach. The examination was performed whilst the patient was in recumbent, supine position. Whilst an indifferent conversation with the patient was carried on the position of the diaphragm was indicated and repeatedly reproduced, the patient being unaware of the moment when the exposures were being made. The cupoles of the diaphragm were approximately at the level of the nipples and the excursions during the respiration were about 1 cm. If the respiration was forced the diaphragm descended some 6 cm. Now the patient was asked to perform the trick which, as he had observed, increased the abdominal circumferences: he pressed his fingers between the two rectus sheaths at a point high up in the epigastrium. It was now observed that both cupoles of the diaphragm immediately descended towards a position corresponding approximately to that to be achieved by a very deep inspiration, that is about 6 cm. below the base line. The excursions of the diaphragm in this position did amount to about 0.5 cm. Also at this stage pictures were taken whilst the patient was unaware of the moment of exposure.

On a later examination pictures were taken by maximum expiration and inspiration before as well as after the patient had performed the trick which descended the diaphragma. See fig. 1—7. Only the right diaphragma vault is visible on the pictures. By frequent fluoroscopy controls it was proved, however, that the left vault moved in the same way as the right, all the time.

Two different positions of the diaphragma are to be registered. The upper position we call *cranial position* and the lower *distal position*.

Subsequent course: The patient went home for 3 months during which time he has been ordered to take a small dose of atropin and barbiturates (isomyl). No outstanding effect of these remedies was to be noted. Some few weeks ago, however, he had for a period of two weeks taken more rest than usual, sleeping every night for at least 12 hours, and during this period the symptoms were almost entirely absent. When he reduced his ration of sleep, however, the symptoms returned. He has forthwith not had any disturbances in connection with his breakfast. He is thus busy until 12 o'clock when he has his luncheon. After this meal he feels his abdominal volume a trifle increased and wants very much to take a nap for half an hour — if he is not awakened by anybody he may then sleep for 3 hours. In the afternoon, when he is busy, he may occasionally experience a feeling of abdominal distension in connection with nausea but as a rule everything runs

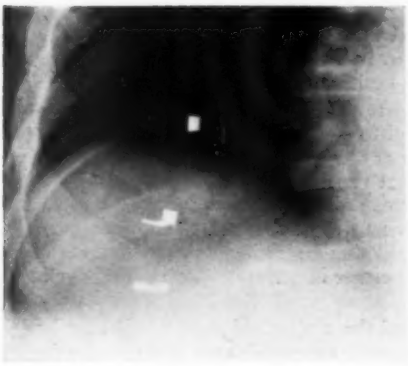

Fig. 1. Cranial position of the diaphragma; the picture was exposured unknown to the patient and during indifferent conversation.

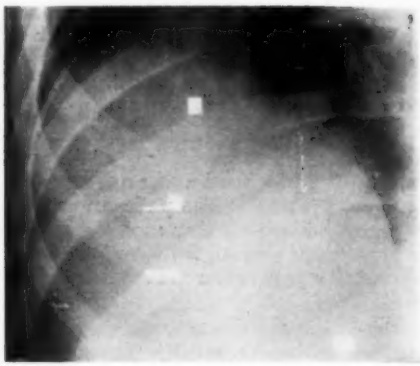

Fig. 2. Cranial position of the diaphragma; maximum expiration.

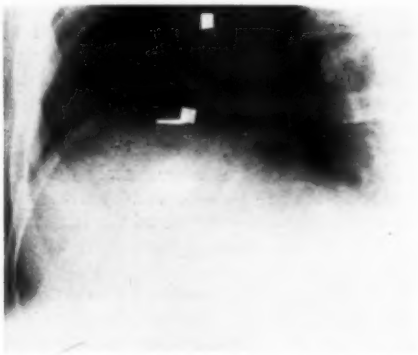

Fig. 3. Cranial position of the diaphragma; maximum inspiration.

smoothly during these hours. At 17 o'clock he has his dinner. In connection with this meal the circumference of the abdomen increases considerably so that he has to unbutton his cloths and assume horisontal position for one or two hours. After this period of rest vomiting may occur, and then he feels relieved, takes a cup of tea and goes to sleep about 20 o'clock. It is thus obvious that his need of sleeping is increased and on the whole the disturbances have always been most pronounced if he for some reason has been unable to get sufficient sleep. He was readmitted to the clinic May 24th. The results of the physical examination were practically identical with those registered during the previous period of observation: his general condition was good, colour normal, blood pressure 120/80, oral cavity, thyroid, lymph nodes, heart, lungs, neurological matters normal. The sedimentation rate was 2, the urine normal, the blood morphology as follows: hemo-

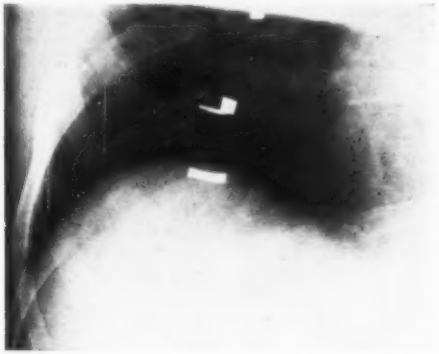

Fig. 4. Distal position of the diaphragma; the picture was exposured unknown to the patient and during indifferent conversation.

Fig. 5. Distal position of the diaphragma; maximum expiration.

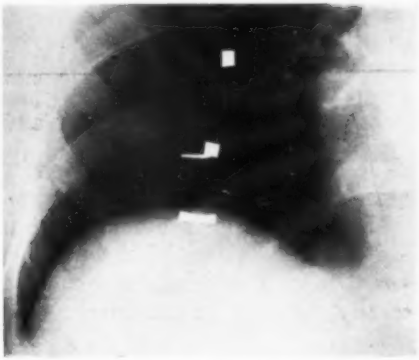

Fig. 6. Distal position of the diaphragma; maximum inspiration.

globin 89 %, red cells 4.5 mill., white cells 4,200, differential count: neutrophiles 34 %, eosinophiles 3 %, basophiles 1 %, lymphocytes 60 %, and monocytes 2 %. The liver functions were normal as far as could be judged from the bilirubin (0.69 mg%), the alkalic phosphatase (7 units), the thymol turbidity test (0.8 units), the Hanger (0), the Takata test, and the bromsulphalein test. Only the galactose tolerance test was forthwith pathological: when given 77 gm. of galactose he excreted about 6 gm. during 3 hours and the peak of the blood sugar curve reached 190 mg%. He was still able to provoke an abdominal distension by means of pressing the tips of his fingers into the abdominal wall beneath the processus ensiformis, at the place of the diastasis between the musc. recti abdominis: the circumference of the abdomen increased immediately about 7 cm. By means of a forced expiration he was able to manage a restitution of the normal abdominal circumference.

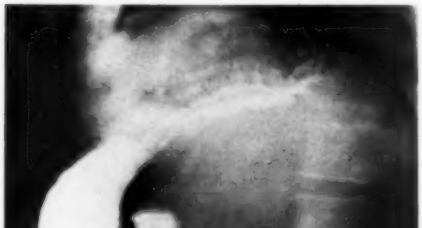

Fig. 7. Picture in lateral position (patient standing) with the ventricle and duodenum filled with contrast (d. p.). No lordosis of the lumbar spine is to be seen. Whilst the distal parts of the stomach are dislocated in ventral direction no similar dislocation of the duodenum is to be observed.

Comment and Discussion

The syndrome of acute abdominal distension presented by this patient is closely similar to that already described by one of us (A.-U.) and although, in our previous communication, we did not venture a more definite guess as to the mechanism involved, the present observation seems to give a satisfactory explanation. The following mechanisms will generally have to be considered when an acute abdominal distension is about.

1. An acute dilatation of the ventricle was ruled out by the roentgen examination as were also aerophagy and increased amount of gas in the bowels (established for instance by means of a volvulus, which under circumstances might be assumed to have been elicited by an abnormal gastrocolic reflex).

2. With regard to the parenchymatous organs the abdominal volume may become increased rather suddenly in the final stage of polycystic kidneys, as witnessed by one of us (A.-U.). This disease was, however, eliminated not only by the urography but also by the absence of any uremia and by the transitory postcibal appearance of the phenomenon. With regard to a cyst of the pancreas it would have been startling if such a cyst was able to change its volume so considerably within a period of minutes and hours. That the pancreas per se transitorily may increase

its volume is a mere theoretical possibility, of which we know no other evidence than the analogous temporary swelling of the parotid glands, as witnessed by one of us (A.-U.) in connection with attacks of ravenous hunger as a sequence after encephalitis. It may be said, however, that the attacks here in question did not occur in connection with hunger and that no roentgenological evidence of any increased size of the pancreas during the attacks was to be elicited. With regard, finally, to the liver it is well known that the liver may be able to increase its volume considerably in quite a short time. But on the one hand such is the case practically only under two conditions, not present in the case here in question (acute cardiac insufficiency, precomatous stage of diabetes), on the other hand, even under such circumstances the sequence of events in the present case was much too rapid to allow an explanation along these lines. It may be objected that a rather sudden expansion of the volume of the liver might be expected to occur as the result of vascular reflexes, elicited on the base of allergy. But it should be maintained that no enlargement of the liver was to be established in this case and that the phenomenon was to be elicited, not only by the ingestion of small amounts of food (the kind of which obviously was of less importance) but also by digital pressure in the pit of the stomach.

The pathological galactose tolerance test might suggest an involvement of the liver, all the more since no Eck-fistula mechanism as represented by varicosities of the oesophagus was to be registered. Yet, the other tests of the liver function were within normal limits and although we consider the galactose tolerance test, if appropriately performed and interpreted as a most reliable evidence of impaired liver function we are inclined to ascribe the result of this test in the present case to quite another factor. Evidence of a gastric hypersecretion along the lines of the ulcer disease was available in the previous history of the patient and it has been emphasized that in such very instances the galactose tolerance test quite often presents pathological features (Ask-Upmark, Ask-Upmark and Berg, Stenstam). It may be added that the general appearance of the patient was in conformity with an ulcer disposition (»pre-ulcer phase») and that engineering more than many other professions seems to be connected with an ulcer disease (it has been estimated, by the pathologists, that peptic ulcers are liable to occur in some 20 % of the population but out of 19 engineers examined by one of us in this regard 8 or possibly 9 had or had had a peptic ulcer).

3. Whilst hence no alteration of the visceral organs of the abdominal cavity could be held responsible for the distension syndrome the result of the roentgen examination seems to furnish an entirely satisfactory explanation. Obviously by means of a reflex, elicited by the entrance into the stomach of food (quite frequently in small amounts) or by

mechanical pressure in the deep region of the cranial epigastrium, an immediate descendence of the average position of the diaphragm was brought about. As a sequence of this changed position the pressure in the abdominal cavity was apparently increased and an augmentation of the circumference of the waist was brought about. This was reasonably facilitated by the diastasis present between the mm. recti abdominis.

With regard to the pathways of this reflex it is of course obvious that the efferent nerves will have to be represented not only by the phrenic nerve but also by the nerves concerned with the muscles regulating the frame in which the diaphragm has to work. The afferent pathway, on the other hand, seems to be more difficult to ascertain but it seems logical to assume the participation of the coeliac plexus centered around the tripod of Haller. Whether this plexus itself or the arteries concerned or the corresponding part of the wall of the ventricle represents the trigger zone cannot be safely stated. That reflexes are to be elicited from this region is well known and evidenced not only from the well known cardiac asystole to be achieved by percussion of this region in rabbits but also by the experimental observations of HEYMANS and not least by the remarkable investigations of REIN about the reactions of the hepatic artery. From clinical point of view we have particularly to remember the fits of unconsciousness to be observed in connection with aneurysms of the splenic artery during pregnancy but also similar attacks which in suitable subjects may be brought about for instance by cold drinks when passing the level of cardia (cf. the »ice-cream headache»). It may well be that this region should be looked upon very much in the same way as the hypersensible carotid sinus. Why the impulses in one case result in unconsciousness, in another case in head-ache and in still another case in this peculiar abdominal distension cannot be said.

Whilst the character of a reflex hence seems to be well established for the syndrome here discussed the question may of course be raised why this reflex is to be elicited in one case and not in another. A lowered threshold has to be assumed anyway and among causes to be considered may be mentioned tetany, encephalitis and migraine. No positive evidence suggesting tetany was to be registered and neither were there any symptoms of encephalitis. It should be admitted, however, that the increased need of sleep which the patient experienced may be compatible with almost any organic lesion of the central nervous system, and that, moreover, not all investigations with bearing on this subject could be carried out (for instance no electro-encephalography). With regard to migraine the patient had no headache and nothing in this connection was to be ascertained with regard to his parents. There are, however, two or three facts which seem to suggest at least a sort of relationship to

migraine. Firstly, the same symptoms, although of transitory character, were to be registered in two of his children. Secondly, when the same syndrome earlier was observed in young girls by one of us, it was quite remarkable to notice how the attacks were confined to the week preceding the menstruation. This periodicity of course, is nothing that is specific to migraine — it is to be registered in numerous other conditions, such as myasthenia gravis, biliary dyskinesia, Addisons disease etc. (ASK-UPMARK). Finally, it was quite obvious that the attacks were confined to a period of the day when the patient was tired, just as his liability of diplopia did ever since childhood. This feature is of course by no means confined to migraine, but to be registered also after head injuries or other damages to the brain. Circumstances prevented a more detailed psychological analysis but although the syndrome did not appear until after the death of his wife it was not felt that this fact should be given undue importance.

Some few weeks after the performance of this paper we have become aware of a most commendable report on the subject, by ALVAREZ, in Archives of Internal Medicine 1949: 84: 217. ALVAREZ has observed the syndrome of non-gaseous abdominal bloating repeatedly. He maintains rightly that the bloating seems to be due to a contraction of the muscles lining the abdominal cavity. Sometimes a lordosis was found to be involved. With regard to the diaphragm ALVAREZ saw a pronounced descent of it in a few cases, although he does not believe it to be the main cause of the bloating. The present paper may perhaps furnish additional evidence on the matter in as much as the following particulars may be stressed:

1. It dealt with a man whilst most of ALVAREZ' cases were females.
2. A definite trigger mechanism was to be elicited.
3. A definite diaphragmatic mechanism was involved.
4. A certain familiar occurrence was to be noted.
5. In several female cases, previously seen by us there was a fairly regular correlation between the appearance of the syndrome and the premenstrual period (when, of course, the nervous threshold is considerably lowered).

Everybody concerned with this interesting syndrome, which may well have affected the poor Queen Draga of Serbia (hysterical pregnancy) should acquaint oneself with the interesting paper of ALVAREZ.

SUMMARY

A case is described, presenting a syndrome of acute abdominal distension, appearing in connection with meals (dinner) but also to be elicited by digital pressure towards the abdominal wall in the midline of the cranial part of the epigastrium. This phenomenon, which has been observed repeatedly on earlier occasions by one of the authors, turned out to be due to a descendence of the diaphragm, established by means of a reflex. The character of this reflex is discussed.

ZUSAMMENFASSUNG

Es wird ein Fall beschrieben, der das Syndrom einer akuten Schwellung des Bauches aufweist, die im Zusammenhang mit den Mahlzeiten (Mittagessen) auftritt, aber auch durch Fingerdruck auf die Bauchwand in der Mittellinie in der oberen Partie des Epigastriums ausgelöst werden kann. Diese Erscheinung, die von dem einen Verf. uns schon früher wiederholt beobachtet wurde, erwies sich als durch eine Senkung des Zwerchfells bedingt, die durch einen Reflex hervorgerufen wird. Die Natur dieses Reflexes wird besprochen.

RÉSUMÉ

Description d'un cas avec syndrome de distension aiguë de l'abdomen, apparaissant après les repas (le dîner) mais pouvant aussi être provoquée par compression digitale de la paroi du ventre, sur sa ligne médiane au haut de l'épigastre. Ce phénomène, déjà observé antérieurement à plusieurs reprises par l'un des auteurs, se révéla dû à un abaissement du diaphragme, causé par un réflexe. La discussion porte sur la nature de ce réflexe.

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DIE NICHTGEFÜLLTE GALLENBLASE[1]

Ein Beitrag zur Röntgenkontrastdarstellung der Gallenblase nach Wasserstoss oder Karlsbader Salz

von

Umberto Cocchi

Es ist eine heute immer noch oft von Klinikern, aber auch von manchem Röntgenologen vertretene Ansicht, dass eine nach Verabreichung eines Gallenkontrastmittels röntgenologisch gut sichtbar gewordene Gallenblase, die sich nach Eigelbgabe gut kontrahiert hat, stets einem völlig normalen Befund entspreche, während eine Nichtfüllung der Gallenblase stets als Zeichen einer Erkrankung der Gallenblase, einer Cholecystopathie anzusehen sei.

Normalerweise gelangt das resorbierte Kontrastmittel mit der von den Leberzellen sezernierten Nativgalle bei geschlossenem Sphinkter Oddi aus der Leber durch den Cysticus in die Gallenblase, wo sie vom Epithel der Gallenblase durch Wasserentzug eingedickt wird. Wie Untersuchungen ergaben, werden täglich etwa 20 ccm Galle pro Kg Körpergewicht von der Leber ausgeschieden und in der Gallenblase kontinuierlich stündlich etwa 6—6.75 ccm Wasser entzogen, nachts nur 1.7 ccm (BRUGSCH und HORSTERS, RAVDIN u. a.). Der Abfluss selbst geht auf dem Lymph- oder Venenweg vor sich. Im Röntgenbild sieht man die kontrastangereicherte Gallenblase dann nach etwa 8—12—16 Stunden im Winkel zwischen der rechten 12. Rippe und der Lendenwirbelsäule; der untere Pol der Gallenblase liegt etwa in Höhe der unteren Kante des 2., nicht selten auch des 3. oder 4. Lendenwirbels. Verabreicht man nun Eigelb (BOYDEN'sche Mahlzeit) oder Fette wie Milch, so tritt nach kurzer Zeit Kontraktion und Entleerung der Gallenblase auf. Dieser Vorgang soll nach einer Reihe von Forschern (BENASSI, BORSCH und BOYDEN, CHIRAY, LEBON und CALLEGARI, WESTPHAL u. a.) neurogen be-

[1] Bei der Red. am 1. XII. 1949 eingegangen.

dingt sein (Vagus), während es sich nach SANDBLOM, VOEGTLIN und IVY um einen hormonalen Effekt handeln soll (Cholecystokinin). Andererseits liessen sich auch psychisch bedingte Kontraktionen der Gallenblase nach Einnahme von Nahrungsmitteln wie Eigelb, Chokolade, Brot usw. in den Mund, ohne dieselben herabzuschlucken, beobachten (NEMOURS-AUGUSTE, GUTMANN).

Je nach dem Zustandekommen bzw. Nichtzustandekommen einer sichtbaren Kontrastfüllung und je nach dem Verhalten der Gallenblasenmotilität unterscheiden wir in der cholecystographischen Diagnostik 5 verschiedene Zustände:

1) gut sichtbarer Schatten der Gallenblase,
2) schwach sichtbarer Schatten der Gallenblase,
3) fehlender Schatten der Gallenblase,
4) gute Kontraktion und Entleerung der Gallenblase,
5) keine Kontraktion der Gallenblase.

Alle diese Veränderungen schliessen aber in keiner Weise weder eine normale noch pathologische Beschaffenheit der Gallenblase aus: wir können sowohl eine gute Füllung der Gallenblase mit guter Kontraktion bei ausgesprochen schweren Veränderungen derselben finden, wie mitunter umgekehrt auch keine Füllung bei scheinbar völlig normaler Beschaffenheit der Gallenblase.

Ein *negatives Füllungsbild* kann durch Veränderungen, die sich sowohl innerhalb wie ausserhalb der Gallenwege abspielen, hervorgerufen werden, es kann dauernd, vorübergehend oder nur vorgetäuscht sein.

Wir finden einen fehlenden Schatten der Gallenblase bei Cholecystitis und Hepatitis, bei entzündlichen Veränderungen im Cysticus, infolge mangelhaften Eindickens in der Gallenblase, wobei sich die Blasenwand, wie von verschiedener Seite operativ kontrolliert werden konnte, zwar makroskopisch intakt erwies, mikroskopisch aber entzündlich verändert war, ferner bei Verhinderung der Kontrastpassage in die Gallenblase infolge Verschluss der Gallenwege durch ein Konkrement oder Tumormassen oder infolge Ausfüllung der Blase mit kleinen Konkrementen und schliesslich bei narbigen Schrumpfungen oder infolge Adhäsionen bedingter Abschnürung im Bereich des Cysticus. Eine Kontrastanreicherung in der Gallenblase kann auch ausbleiben, falls bei peroraler Verabreichung des Kontrastmittels eine Stenose im Bereich der oberen Speisewege und des Magens besteht, z. B. bei Pylorusstenose, ferner bei mangelhafter Resorption des Kontrastmittels im Duodenum. Fehlen der Schattenbildung ist auch bei Magen- und Dünndarmulkus, bei Pankreatitis oder Pankreaskarzinom, bei Diabetes mellitus, bei Steinerkrankungen im Bereich der Harnwege und in seltenen Fällen auch

beim Basedow beobachtet worden. Die Nichtfüllung der Gallenblase kann also einerseits organisch andererseits wohl auch durch reflektorische Nervenstörungen bedingt sein.

Eine nichtgefüllte Gallenblase kann mitunter auch infolge abnorm veränderter Lokalisation vorgetäuscht sein. So wurde von uns in einem Fall zuerst ein negatives Füllungsbild festgestellt; erst bei der nachfolgenden Dickdarmuntersuchung mittels Kontrasteinlauf konnte die steingefüllte Gallenblase im kleinen Becken unterhalb des rechten Ileosakralgelenkes beobachtet werden. Es bestand hier eine Ptose sämtlicher Abdominalorgane.

Wichtig für die Forschung und Praxis ist in dieser Hinsicht die Kontrolle des Röntgenbefundes durch den Operationsbefund. Eine Zusammenstellung über die Ergebnisse der Röntgenuntersuchung der Gallenblase und des Operationsbefundes finden wir beispielsweise auf Tabelle 1, die eine Übersicht über 217 Cholecystographien gibt, von denen 82 in der Chirurgischen Universitätsklinik Zürich operativ kontrolliert wurden (Hotz). Die Untersuchungen wurden z. Zt. mit Oraltetragnost durchgeführt. 123 mal (56.7 %) fand sich eine gute resp. schwache Füllung der Gallenblase und 94 mal (43.3 %) keine Füllung der Gallenblase. In den 156 Fällen, in denen klinisch Anhaltspunkte für eine Erkrankung der Gallenblase und der Gallenwege vorlag, wurde 72 mal (46.2 %) eine gute resp. schwache Füllung festgestellt, während 84 mal (53.8 %) keine Füllung stattfand. In den 61 Fällen mit ausserhalb der Gallenwege gelegenen Prozessen wurde 51 mal (84 %) Füllung und 10 mal (16 %) keine Füllung beobachtet.

Unter den 82 operativ kontrollierten Patienten fanden sich 25 mit guter Füllung der Gallenblase, 8 mit schwacher Füllung und 51 ohne Schattenbildung. Unter den erstgenannten 25 Patienten stellte man im Laufe der Operation bei 8 Patienten eine gesunde Gallenblase fest; es handelte sich klinisch in 5 Fällen um Verdacht auf Gallenblasenaffektion und in 3 Fällen um Pankreatitis. Bei den restlichen 17 Patienten wurde bei der Operation eine Cholelithiasis festgestellt, die allerdings schon vor der Operation röntgenologisch diagnostiziert werden konnte. Unter den 8 Fällen mit schwacher Gallenblasenfüllung fand sich operativ selten eine intakte Gallenblase; zweimal wurde hier ein Karzinom der Gallenwege angetroffen, von denen das eine an der Papilla Vateri und das andere an der Einmündungsstelle des Ductus cysticus in den Choledochus gelegen war, und 6 mal Konkremente in der Gallenblase, im Cysticus oder im Choledochus. Unter den 49 Fällen ohne Gallenblasen-Kontrastfüllung wurden 3 mal (rund 6 %) intakte Gallenwege resp. eine intakte Gallenblase gefunden (zweimal handelte es sich klinisch um unklare Bauchbeschwerden und einmal um Karzinommetastasen in der Leber), in den übrigen Fällen (94 %) handelte es sich hauptsächlich um Gallen-

Tabelle 1

Übersicht über 217 Cholecystographien mit operativer Kontrolle in 82 Fällen (nach Hotz)

Klinische Diagnose	Fälle	Füllung der Gallenblase			Operationsbefund
		gut	schwach	keine	
Cholecystopathie	25	1	4	20	
	5	—	—	5	Cholecystitis ohne Konkremente
Verdacht auf Cholecystopathie	29	15		14	
	5	5		—	Normale Gallenblase
Unklare Bauchbeschwerden	26	22		4	
	2	—		2	Normale Gallenblase
Cholelithiasis	59	17	6	36	Konkremente, sie wurden in 16 Fällen schon auf der Röntgenleeraufnahme u. in 19 Fällen im Cholecystogramm festgestellt, 24 mal erst operativ.
Primäre u. sekund. Malignome der Leber- u. Gallenwege	4	—	2	2	Karzinom d. Papilla Vateri, des Ductus choledoch., der Gallenblasenwand u. Lebermetastase.
Verdacht auf Malignom	1	—	—	1	
Pankreaskarzinom	2	—	—	2	1 mal Verlegung d. Gallengänge durch grossen Tumor m. Lebermetastasen
Pankreatitis	3	3	—	—	Normale Gallenblase
	1	1	—	—	
Verdacht auf Pankreatitis	2	2	—	—	
Ulcus ventriculi	5	5	—	—	
	1	—	—	1	Ulc. perfor., subphren. u. Pankreasabszesse
Ulcus duodeni	11	10	1	—	
Ulcusbeschwerden p. op.	3	3	—	—	
	1	—	—	1	Ausgedehnte Adhäsionen
Ulcusverdacht	3	2	—	1	
Magenbeschwerden	2	2	—	—	
Hyperazidität	6	4	—	2	
Anazidität	3	2	—	1	
Appendizitis	7	6	—	1	
Askariden	2	2	—	—	
Magenkarzinom	1	—	—	1	
Nephroptose, infiz. Hydronephr., Kolizystit., akute ödem. Zystit., Verdacht auf Nierenstein	je 1	1	—	—	
Akute häm. Zystit.	1	—	1	—	
Nierenstein	2	—	2	—	

steine (36 Fälle = 73 %), Gallenwegs- oder Pankreaskarzinom, Cholecystitis, Adhäsionen und Abszessbildungen im Abdomen.

Insgesamt finden wir also unter den 68 operativ verifizierten Fällen mit Erkrankungen des Gallenwegssystems 17 (25 %) mit gut gefüllter Gallenblase, 8 (rund 12 %) mit schwach gefüllter Blase und 43 (rund 63 %) mit fehlender Schattenbildung.

Interessant sind in dieser Hinsicht, im Vergleich zu den Ergebnissen der Gallenblasenuntersuchungen, die für die Chirurgische Klinik gemacht wurden, diejenigen einer internistischen Klinik (WEYLAND und MAIER). Hier erhalten wir, nach Verabreichung von Jodobil, gute Kontrastfüllung der Gallenblase in 67 %, schwache Füllung in 17 % (zusammen 84 %) und gar keine Füllung in nur 16 %.

Ein Ausbleiben der Gallenblasenfüllung bei normalen Operationsbefund erhalten wir demnach bei rund 6 %; in einem Fall war das Ausfallen der Füllung durch Lebermetastasen bedingt, in den beiden anderen Fällen könnte es sich möglicherweise um zwar makroskopisch intakte aber mikroskopisch entzündliche Blasen gehandelt haben. Ähnliche Prozentsätze finden sich auch im Schrifttum angegeben. So bemerkten z. B. DANN und KORITSCHONER bei der Prüfung der Gallenblasen-Entleerung von 21 gesunden Individuen in 2 Fällen keine Füllung der Blase (10 %), MORALES und SWEDBERG unter 303 operierten Fällen in 4 % und KRAUS unter 72 operierten Fällen in 7 % keine Füllung der Blase. Der Grund für diese Nichtfüllung kann jedoch nicht allein in einer entzündlichen Veränderung der Blasenschleimhaut liegen, haben wir doch genügend Beweise für positive Gallenblasenfüllungen bei pathologisch-anatomisch festgestellten Entzündungen der Schleimhaut. Die Ergebnisse der cholecystographischen Untersuchung müssen demnach von verschiedenen Faktoren abhängen, die das Zustandekommen bezw. Nichtzustandekommen einer Füllung beeinflussen.

Ein wichtiger Faktor bildet hierbei das verabreichte *Kontrastmittel.* Vergleichende Untersuchungen zeigten nämlich, dass eine Verbesserung der Schattenbildung schon durch Wechseln des Kontrastmittels möglich ist. So fand z. B. QUASTLER bei 100 Patienten eine gute Füllung der Gallenblase nach Jodtetragnost in 40 % der Fälle, nach Priodax (= Biliselectan) hingegen in 68 %, während die Prozentzahlen der Aufnahmen mit schwacher Füllung demgegenüber von 22 % auf 16 % und diejenigen ohne Schattenbildungen von 38 % auf 16 % abnahmen. Von 660 von WICKBOM peroral mit Tetrajodphenolphthalein durchgeführten Gallenblasenuntersuchungen wiesen 130 ein negatives Füllungsbild auf. Von diesen 130 füllten sich bei einer nochmaligen Untersuchung mit Biliselectan 40 Fälle (über 30 %), wobei jetzt bei 10 dieser Fälle Konkremente festgestellt werden konnten. In 90 Fällen blieb die Gallenblase wiederum ungefüllt.

Tabelle 2

Zusammenstellung der 88 nichtgefüllten Gallenblasen hinsichtlich der Diagnose und der später auftretenden Verbesserung der Schattendichte

Klinische Diagnose	Anz. Fälle	Kontrast im Colon	Konkrem. auf Leeraufnahme	Nachträgl. mit Wasser	Füllung Karlsb.	Konkrem. sichtbar
a. *Keine Füllung der Gallenblase nach peroraler Kontrasteinnahme.*						
Cholelithiasis	31	4	5	5	1	1
Cholecystopath.	13	—	—	1	2	1
Cholecystitis	9	2	—	2	—	—
Schmerzen im Abdomen	4	1	1	1	—	—
Tumor im Abdomen	3	—	—	—	2	—
Leberzirrhose	2	—	—	1	—	—
Hepatitis	1	—	—	—	—	—
Pankreatitis	1	—	—	—	—	—
Cystopyelitis	1	1	—	—	—	—
Prostata-Metast.	1	—	—	—	—	—
Verschlussikterus	1	—	—	—	—	—
Coronarinsuffiz.	1	—	—	—	—	—
	68	8	6	10	5	2
b. *Schwach gefüllte Gallenblase nach peroraler Kontrasteinnahme.*						
Cholelithiasis	9	—	—	2	2	3
Cholecystopathie	7	—	—	2	2	1
Ikterus	1	—	—	1	—	—
Schmerzen im Abdomen	1	—	—	—	1	—
Ulcus pept.	1	—	—	1	—	—
Paratyphusbazillenträger	1	—	—	1	—	—
	20	—	—	7	5	4

Mitunter findet man sogar bei Wiederholung der Untersuchung mit dem gleichen Kontrastmittel Füllung der Gallenblase. Wir konnten diesen Vorgang in 3 Fällen zweimal beobachten, WEYLAND und MAIER ebenso zweimal in 7 Fällen nach zwei- oder dreimaliger Wiederholung, HEFKE hingegen bei 30 Fällen nur einmal. FRIEDMAN und FRIEDMAN erzielten bei 472 Cholecystographien in 23.5 % ein negatives Füllungsbild, bei Wiederholung der Untersuchung nur in 11.6 %.

Durch die in den letzten Jahren durchgeführten Untersuchungen verschiedener italienischer Forscher wurde unsere Aufmerksamkeit auf einen weiteren Faktor gerichtet, der ebenfalls eine Rolle bei der Kontrastfüllung der Gallenblase spielt. Nachdem schon 1928 BENASSI bei Versuchen an Hunden nach *peroraler Zufuhr von gewöhnlichem Leitungswasser* eine leichte Verkleinerung des Blasenschattens beobachtete, konnte später auch beim Menschen einerseits Füllung einer ursprünglich

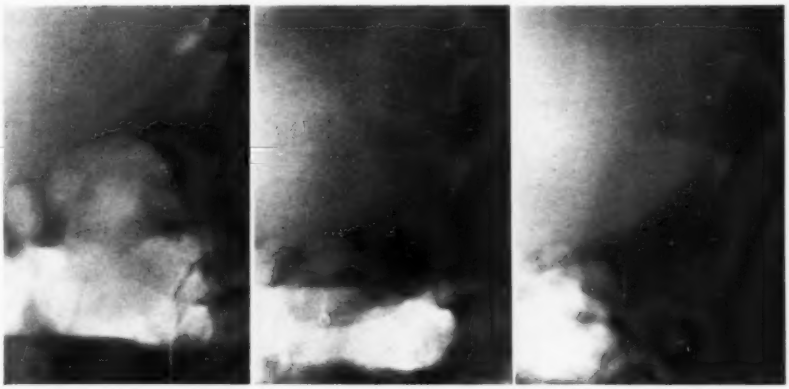

Abb. 1 a. Abb. 1 b. Abb. 1 c.

Abb. 1. *Cholecystogramm bei 35 jährigem Patient mit klinischer Diagnose Cholecystitis.* a = 1. Aufnahme 14 Stunden nach peroraler Verabreichung von Jodobil: keine Füllung sichtbar. b = 10 Minuten nach Wassertrinken: gute Füllung einer auf dem Colon reitenden Gallenblase. c = 40 Minuten nach Eigelbgabe: Gute Kontraktion der Gallenblase.

nicht gefüllten Gallenblase oder andererseits Verbesserung der Schattendichte und mässige Abnahme der Grösse einer anfangs nur schwach gefüllten Blase nach peroraler Wasserzufuhr festgestellt werden (VITALE 1937).

In den letzten Monaten wurde auch am Zürcher Röntgeninstitut systematisch in sämtlichen Fällen mit nichtgefüllter oder nur schwach gefüllter Gallenblase zusätzlich Wasser und später statt dessen auch Karlsbader Salz peroral verabreicht. Insgesamt handelt es sich bisher um 91 Versuche; 57 mit Wasser und 34 mit Karlsbader Salz.

Den Patienten war am Abend vor der Untersuchung entweder Jodobil oder Priodax peroral, in einigen Fällen auch Oraltetragnost verabreicht worden und die erste Aufnahme in nüchternem Zustand am nächsten Morgen nach etwa 13—14 Stunden vorgenommen. Blieb das erste Röntgenbild negativ oder zeigte sich nur eine schwache Füllung der Gallenblase, so wurden anschliessend dem Patienten 200 ccm gewöhnliches Leitungswasser zum Trinken gegeben. Statt dessen wurde auch ein Teelöffel Karlsbader Salz in 50 ccm Wasser aufgelöst verabreicht. 10 Minuten später wurde die zweite Aufnahme vorgenommen. Dann wurden 2 Eigelb gegeben und 40 Minuten später die dritte Aufnahme gemacht.

In 69 Fällen wurde auf der ersten Aufnahme, 14 Stunden nach Verabreichung des Kontrastmittels, *keine Füllung* der Gallenblase festgestellt (Tab. 2). Nach Wasser oder Karlsbader Salz füllten sich hingegen zusätz-

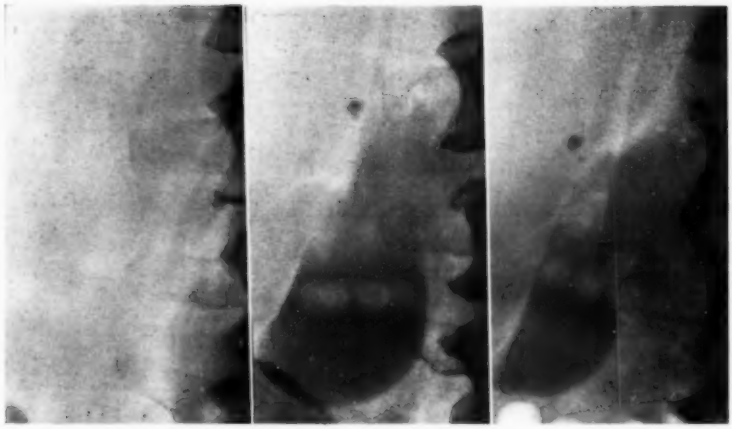

Abb. 2 a. Abb. 2 b. Abb. 2 c.

Abb. 2. *Cholecystogramm bei 48 jähriger Patientin mit klinischer Diagnose: fragliche Cholecystopathie.* a = 1. Aufnahme 14 Stunden nach peroraler Verabreichung von Priodax: keine sichere Füllung der Gallenblase, b = 10 Minuten nach Karlsbader Salz: gute Füllung und Darstellung von Konkrementaussparungen, c = 40 Minuten nach Eigelbgabe: gute Kontraktion, die Konkremente sind gut sichtbar.

lich noch 15 Blasen (rund 22 %), und zwar nach Wasserzugabe von 40 Fällen 10 (25 %) (Abb. 1), nach Zusatz von Karlsbader Salz von 28 Fällen 5 (18 %), wobei sich in zwei Fällen Konkremente darstellen liessen. Diese traten einmal nach Karlsbader Salz (Abb. 2) und das andere Mal nach Wasser auf (Abb. 3). Die Schattendichte war nach Wassergabe in 6 Fällen schwach und in 4 gut, nach Karlsbader Salz dreimal schwach und zweimal gut. In einem Fall, bei dem die Untersuchung wiederholt werden sollte, war schon, im Gegensatz zur ersten Untersuchung, auf der ersten Aufnahme der zweiten Untersuchung eine gute Füllung der Gallenblase feststellbar.

Nur 4 dieser Fälle wurden einem operativen Eingriff unterzogen (Tab. 3), von denen sich bei 3 auch nach Wassertrinken keine Füllung der Gallenblase einstellte, während sich im 4. Fall nach Wassergabe eine schwache Füllung der Blase zeigte (Abb. 3). In diesem Fall wurden auf der 2. Aufnahme am Blasenboden kleine Aussparungen sichtbar, die auf der 1. Aufnahme noch nicht bemerkt wurden, und die auch noch auf der 3. Aufnahme zu sehen sind. In sämtlichen 4 Fällen wurden bei der Operation Konkremente in der Gallenblase gefunden sowie Entzündung der Blasenwand.

In 6 Fällen wurden schon auf der Leeraufnahme Steinschatten im

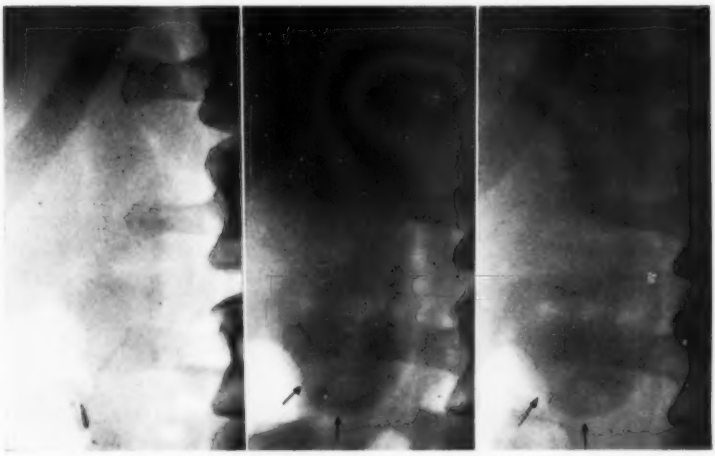

Abb. 3 a. Abb. 3 b. Abb. 3 c.

Abb. 3. *Cholecystogramm bei 33 jähriger Patientin mit Gallensteinkoliken.* a = 1. Aufnahme 14 Stunden nach peroraler Verabreichung von Priodax: keine sichere Füllung, b = 10 Minuten nach Wassertrinken: schwache Füllung einer normal grossen Gallenblase mit 2 feinen Konkrementaussparungen am Blasenboden (Pfeile), c = 40 Minuten nach Eigelbgabe: Kontraktion der schwachgefüllten Blase, Aussparungen noch sichtbar (Pfeile). Operation ergibt Konkremente und Cholecystitis (Chir. Univ. Klin. Zürich, Dir.: Prof. BRUNNER).

Blasenbereich festgestellt, eine Füllung konnte hier nie erzielt werden. In 8 weiteren Fällen, bei denen ebenfalls nie eine Füllung der Gallenblase erreicht werden konnte, konnte das Kontrastmittel im Dickdarm, teilweise als feine, kontrastdichte Flöckchen beobachtet werden. In 2 dieser letzteren Fälle wurden operativ Konkremente festgestellt.

Eine *schwache Füllung* wurde in 20 Fällen angetroffen. Eine Verbesserung der Schattendichte wurde in 12 Fällen (rund 60 %) erzielt, und zwar nach Wassergabe in 7 von 14 Fällen (50 %) und nach Karlsbader Salz in 4 von 6 Fällen (83.3 %), wobei in je 2, sei es mit Wasser- oder Karlsbader Salzzugaben behandelten Fällen Konkrementaussparungen in der 2. Aufnahme sichtbar wurden (Abb. 4). Operativ konnten zwei Fälle kontrolliert werden (Tab. 3).

Wie Tabelle 4 zeigt, besteht hinsichtlich der Wirkungskraft kein wesentlicher Unterschied zwischen der Gesamtheit der Fälle, die mit Wasser und derjenigen, die mit Karlsbader Salz behandelt wurden (31.4 % gegenüber 29.4 %). Soweit die wenigen Fälle mit Karlsbader Salz aber eine Beurteilung zulassen, scheint die Wirksamkeit hier bei den

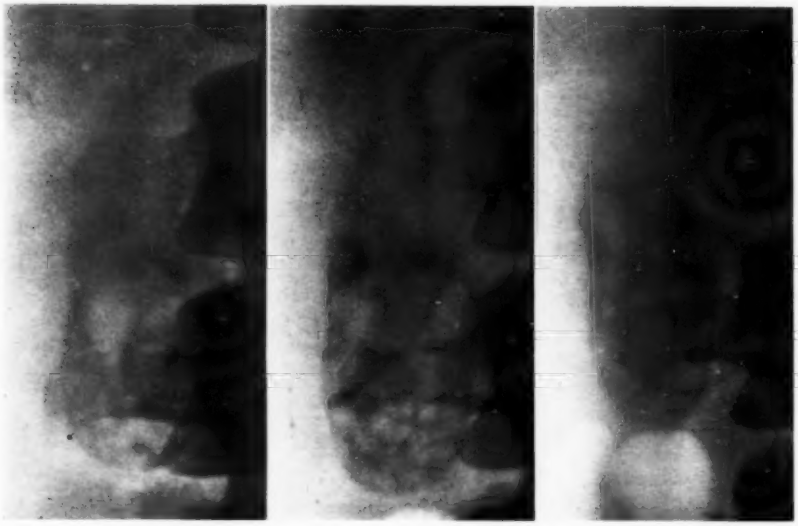

Abb. 4 a. Abb. 4 b. Abb. 4 c.

Abb. 4. *Cholecystogramm bei 32 jähriger Frau mit klinischer Diagnose: Fragliche Cholecystitis oder Cholelithiasis.* a = 1. Aufnahme 14 Stunden nach peroraler Einnahme von Jodobil: schwache Füllung mit einigen Luftblasen im Blasenschatten. Kein Steinschatten sicher nachweisbar, b = 10 Minuten nach Wassertrinken: Bessere Kontrastdichte der Blase, am Blasenboden multiple geschichtete kleine Konkremente sichtbar, c = 40 Minuten nach Eigelbgabe: Kontraktion der Blase, die Konkrementschatten nur noch undeutlich sichtbar. Die Operation bestätigt das Vorhandensein von Konkrementen.

Fällen grösser zu sein, bei denen schon auf der ersten Aufnahme eine schwache Füllung der Blase sichtbar ist (rund 83 % gegenüber 50 %). Ist die Gallenblase schwach gefüllt, so erreicht man sowohl nach Verabreichung von Wasser wie von Karlsbader Salz in weitaus mehr Fällen bessere Kontrastdichte als in den Fällen, in denen anfangs die Gallenblase überhaupt nicht zur Darstellung gelangte.

Insgesamt finden wir also bei unseren 88 Fällen 27 mal, d. h. in fast 31 % eine Verbesserung der Schattendichte bezw. eine Füllung der Gallenblase überhaupt, wobei sich in 6 Fällen (6.8 %) vorher nicht sichtbare Konkremente darstellen liessen (10 % in Fällen mit klinischer Diagnose Cholelithiasis).

Als zweite Wirkung stellen wir sowohl nach Verabreichung von Wasser wie Karlsbader Salz eine *Verkleinerung der Gallenblasengrösse* fest. Diese Verkleinerung betrug 0.2—1.2 cm, durchschnittlich etwa 0.5 cm bei 7 der 12 Fälle, bei denen eine Zunahme der Kontrastdichte

Tabelle 3

Vergleich zwischen klinischem, röntgenologischem und operativem Befund in sechs Fällen

Klinische Diagnose	Cholecystographie			Operationsbefund
	1. Aufn.	n. Wasserzugabe	n. Eigelb	
Cholelithiasis	—	—	—	Konkremente + Cholecystitis
Cholelithiasis	—	—	—	Konkremente + Cholecystitis
Cholecystitis	—	—	—	Konkremente + Cholecystitis
Cholelithiasis	—	+ (Konkrem. sichtbar)	kontrah.	Konkremente + Cholecystitis
Cholelithiasis? ..... Cholecystitis?	+	++ (Konkrem. sichtbar)	kontrah.	Konkremente
Cholelithiasis	+	+	kontrah.	Konkremente + Cholecystitis (mikroskop.)

— = negatives Füllungsbild.
\+ = schwaches Füllungsbild.
++ = gutes Füllungsbild.

Tabelle 4

Kontrastanreicherung und Verbesserung der Kontrastdichte nach Verabreichung von Wasser und Karlsbader Salz

Röntgenbefund nach peroraler Kontrastmitteldarreichung	Anz. der Fälle	mit *Wasser*			mit *Karlsbader Salz*			Total	%
		Anz.	posit.	%	Anz.	posit.	%		
Keine Füllung.....	68	40	10	25 %	28	5	17.9 %	15	22.1 %
Schwache Füllung.....	20	14	7	50 %	6	5	83.3 %	12	60.0 %
	88	54	17	31.4 %	34	10	29.4 %	27	30.7 %

auf der 2. Aufnahme zu bemerken war. Doch war diese Verkleinerung auch bei 5 der 8 Fälle feststellbar, bei denen keine Zunahme der Kontrastdichte bestand; sie betrug hier durchschnittlich 0.3 cm. Nach Verabreichung von 2 Eigelb konnte man andererseits eine Kontraktion der Gallenblase in 9 der 12 zuerst genannten Fälle um 0.5—2.8 cm, durchschnittlich um 1.5 cm feststellen, unter den 8 anderen Fällen 7 mal durchschnittlich um 1.4 cm. In den 15 Fällen, in denen die 1. Aufnahme nicht gefüllt war und eine Kontrastanreicherung der Gallenblase erst nach Wasser oder Karlsbader Salz auftrat, sah man Kontraktion der Blase in allen 15 Fällen um 0.5—4.5 cm, durchschnittlich um 1.8 cm. Insgesamt bewirkte Verabreichung von Wasser oder Karlsbader Salz Verkleinerung in 12 von 20 Fällen (60 %) um durchschnittlich 0.6 cm und

Verabreichung von 2 Eigelb Kontraktion der Gallenblase in 32 von 35 Fällen (91.4 %) um durchschnittlich 1.8 cm. *Die Verkleinerung der Gallenblase nach Wasserzugabe oder Karlsbader Salz geht demnach nicht immer mit einer Zunahme der Schattendichte parallel; sie ist immer geringer als nach Eigelbgabe.*

Ein Sichtbarwerden einer nichtgefüllten Gallenblase erst nach Verabreichung von Eigelb, wie es BECCHINI bemerkt haben will, konnte bei uns *nie* beobachtet werden.

Eine bessere Schattenbildung der Gallenblase und Abnahme der Grösse konnte auch nach peroraler Einnahme von Bariumbrei bei Magenuntersuchungen (CASATI u. a.) sowie bei Dickdarmeinläufen (BUISSON) in dem Augenblick bemerkt werden, in welchem die Bariumsäule in den Bereich der Flexura hepatica gelangte. Hat sich die Gallenblase infolge Eigelbgabe schon kontrahiert, so kann andererseits perorale Bariumverabreichung wiederum eine Grössenzunahme der Blase bewirken (RONCORONI). Eine bessere Schattendichte und Sichtbarwerden einer Gallenblase liess sich auch bei magenresezierten Patienten nach Wasserzugabe feststellen (CORSERI). An der normal gefüllten Gallenblase ruft hingegen die Wasserzugabe keine Wirkung auf die Schattendichte oder Blasengrösse hervor.

Der Wasserstoss wie auch die Verabreichung von Karlsbader Salz bewirken demnach beide eine bessere Kontrastanreicherung der Gallenblase. Dies kann einerseits dadurch bedingt sein, dass sich überhaupt keine kontrastangereicherte Galle in der Blase befindet, da sie durch Spasmus des Sphinkters, den LÜTKENS und IVY im Cysticus beobachtet haben, zurückgehalten wird, oder dass sich die Blase mit Galle gefüllt hat, letztere sich aber infolge mangelhafter Wasserresorption in unkonzentriertem Zustand befindet, so dass die für ein Sichtbarwerden nötige Dichte nicht erreicht wird. Das Vorkommen von äusserst schwach sichtbaren Gallenblasen, die mitunter erst erkannt werden können wenn die Lokalisation derselben durch den Wasserstoss oder die Verabreichung von Karlsbader Salz ersichtlich wird, spricht aber zugunsten der 2. Annahme.

Normalerweise vermag die Gallenblase die in sie einfliessende Galle innerhalb von 2 Stunden auf das 3—4 fache einzudicken (BRUGSCH und HORSTERS). Die Eindickung, die, wenn auch in geringerem Masse, in den extrahepatischen Gallenwegen ausserhalb der Blase möglich ist, ist um so stärker, je geringer die Konzentration der produzierten Lebergalle ist. Die Resorptionsgrösse sinkt dann mit zunehmender Konzentration der Blasengalle und hört auf, wenn die Galle eine Konzentration von etwa 20 % Trockensubstanz erreicht hat.

Wie unsere Fälle aber zeigen, kann bei einer gewissen Anzahl von Gallenblasen die Wasserresorption verzögert sein, ohne dass die resorp-

tive Kraft der Blasenschleimhaut überhapt aufgehoben zu sein braucht. Diese verzögerte Resorption scheint hier, wie es die Untersuchungen von VITALE ergaben, hauptsächlich durch leichtere entzündliche Veränderungen der Schleimhaut bedingt zu sein.

Tritt im Abdomen nun plötzlich eine Drucksteigerung durch Einführung einer grösseren Wassermenge auf oder wird Karlsbader Salz verabreicht, so führt dies, wie BRUGSCH und HORSTERS im Tierexperiment zeigen konnten, reflektorisch zu einer kurzandauernden stärkeren Drucksteigerung in der Gallenblase infolge Tonuserhöhung der Blasenwand, ohne dass es indessen zur Gallenblasenentleerung kommt. Die Tonuserhöhung ist auch röntgenologisch in etwa zwei Drittel der Fälle in Form der mässigen Verkleinerung der Blasenbreite sichtbar, die allerdings nicht derartige Masse annimmt, wie wir es anschliessend an die Eigelbgabe während der Blasenentleerung beobachten können. Als Folge der plötzlichen Drucksteigerung in der Blase finden wir auf unseren Röntgenbildern in den nächsten 5—10—15 Minuten eine zunehmende Schattendichte infolge Einsetzens der bis dahin ruhenden Resorption. Diese kann dann sehr schnell vor sich gehen. Schon vor Jahren konnten ROUS und MCMASTER experimentell die Zeitdauer der Resorption nachweisen, indem sie an Hunden am Blasenboden einen künstlichen Ausgang schufen und die Konzentration der Galle nach dem einfachen Durchgang durch die Blase massen. Die Galle wurde in dieser kurzen Zeit auf das 2.3 bis 4.8 fache konzentriert. Eine Tonuserhöhung braucht aber andererseits, wie wir es sahen, nicht immer sogleich mit Wasserresorption aus der Blase zusammengehen.

Weniger wahrscheinlich erscheint es, dass die Zunahme der Schattendichte oder das plötzliche Auftreten einer bis dahin nicht darstellbar gewesenen Gallenblase nach Verabreichung von Wasser oder Karlsbader Salz durch plötzliche Ausschwemmung von gefärbter Galle aus den Leber bedingt sei, wie es von VITALE angenommen wird, da die Cholerese beim Menschen nicht durch Wasser gefördert wird (BARBERA, BRUGSCH und HORSTERS), sondern hauptsächlich durch Eiweissabbauprodukte und Salzen wie Magnesium- und Natriumsulfat (JACOBSON und GYDESEN), vielleicht auch durch Vagusreizung (EIGER). Wasser sowie Karlsbader Salz bewirken aber beide, wie wir es im Röntgenbild beobachten konnten und mit Karlsbader Salz auch im Tierversuch, Tonuserhöhung in der Gallenblase, während die Cholagogie weder von dem einen noch anderen Mittel beeinflusst wird. *Als Auslöser der verzögerten Galleneindickung müssen wir demnach einzig die Tonuserhöhung ansehen.*

Wie wir zeigen konnten, stellen diese beiden Methoden ein wertvolles Hilfsmittel bei der Röntgenuntersuchung der Gallenblase dar. Ein negatives Füllungsbild ist demnach nicht in allen Fällen als konstanter Zustand anzusehen, sondern lässt sich in etwa einem Viertel der Fälle

noch in ein positives umwandeln. Ein schwaches Füllungsbild kann ferner in über der Hälfte der Fälle in ein kontrastdichteres umgewandelt werden. Es besteht hier eine Verzögerung der Wasserresorption der in die Gallenblase gelangten Lebergalle, die wohl zum grossen Teil durch leichte oder auch stärkere entzündliche Veränderungen der Blasenschleimhaut bedingt ist. Die Methoden gestatten uns, einerseits ein besseres Urteil über die Passageverhältnisse in den extrahepatischen Gallenwegen, nach Ausschluss von Schädigungen des Leberparenchyms, abzugeben und mit ziemlicher Sicherheit einen Verschluss auszuschliessen und andererseits eine Verbesserung der Darstellung von Konkrementen in der Gallenblase zu bewirken.

ZUSAMMENFASSUNG

Nach Aufzählung der Gründe für das Nichtzustandekommen einer Kontrastdarstellung der Gallenblase und Betrachtung der von Hotz durchgeführten Untersuchung von 217 Cholecystographien am Zürcher Universitätsröntgeninstitut, von denen 82 an der Chirurgischen Universitätsklinik operativ kontrolliert wurden, werden die Methoden erwähnt, die zu einer Verbesserung der Darstellbarkeit der kontrastgefüllten Gallenblase führen (Wechsel des Kontrastmittels, Wiederholung der Untersuchung). Schliesslich werden zwei Methoden besprochen, bei denen sowohl nach *Wasserstoss* wie nach Verabreichung von *Karlsbader Salz* in einem Viertel der Fälle ein ursprünglich »negatives Füllungsbild» in ein positives und ein »schwaches Füllungsbild» in über der Hälfte der Fälle in ein kontrastreicheres umgewandelt wird. Dadurch wurde in fast 7 % der Fälle die Darstellung von anfänglich röntgenologisch nicht sichtbaren Konkrementen möglich gemacht.

SUMMARY

The causes of the non-visualization of the opacified gallbladder and Hotz' studies of 217 cholecystographies carried out at the Roentgen Department of the University Hospital in Zürich are discussed. In 82 of these cases in which the patient was operated on at the Surgical Department of the University Hospital, the findings at the operation confirmed the radiologic diagnosis. In addition, the methods are discussed which allow a better visualization of the gallbladder (trial of another opaque medium, re-examination of the patient in cases in which the diagnosis was missed at the first examination) giving particular consideration to the value of the »water test› and of the administration of Carlsbad salt in the radiologic study of the gallbladder. It is stated that each of these two methods had a concentrating effect upon the gallbladder, producing in one fourth of the cases where the first cholecystogram was »negative», a positive cholecystogram, and »denser shadows› in more than one half of the cases which had shown poor concentration of the opaque medium. It is pointed out that these methods revealed calculi in 7 per cent of the cases, in which the diagnosis had been missed in the first cholecystogram.

RÉSUMÉ

L'auteur commence par énumérer les raisons pour lesquelles une vésicule biliaire peut rester invisible à la cholécystographie par opacification, puis il s'arrête aux recherches faites par Hotz, à l'Institut Radiologique Universitaire de Zurich, sur 217 cholécystographies dont 82 furent contrôlées opératoirement à la clinique chirurgicale de

l'Université, et enfin il cite les méthodes qui améliorent la mise en évidence de la vésicule remplie d'une substance opaque (utilisation d'un autre produit opacifiant, répétition de l'examen). Pour finir il discute de deux procédés grâce auxquels, après un »choc hydrique» aussi bien qu'après l'administration de sel de Carlsbad, on voit dans un quart des cas une image primitivement »négative» devenir positive, et dans la moitié des cas une image de faible remplissage se transformer en une image à meilleur contraste. De la sorte il fut possible dans presque 7 % des cas de faire apparaître des concrétions qui d'abord étaient demeurées invisibles aux Rayons Roentgen.

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IMPORTANT NOTICE

6th INTERNATIONAL CONGRESS OF RADIOLOGY, 1950

It has been decided to extend until April 1st the date by which offers of papers to be read before the Congress must be submitted. Such offers must be accompanied by the abstract and the application for registration as a member of the Congress, and should be sent to the Secretary-General, 45 Lincoln's Inn Fields, London, W. C. 2.

Dr. J. W. McLAREN, Secretary-General.

FROM THE ANATOMICAL INSTITUTE, UNIVERSITY OF OSLO, NORWAY (CHIEF: PROFESSOR JAN JANSEN, M. D.) AND THE ROENTGEN DEPARTMENT OF THE UNIVERSITY HOSPITAL (CHIEF: PROFESSOR TORLEIF DALE, M. D.). AND THE HEALTH DEPARTMENT, SECTION OF MASS ROENTGENOGRAPHY (CHIEF: DR. OTTO GALTUNG HANSEN)

THE DEVELOPMENTAL ANATOMY OF THE HEART AND THE ETIOLOGY OF CONGENITAL HEART DISEASE[1]

by

Johan Torgersen

The aim of this study is not to give a critical review of the literature concerning the normal and abnormal development of the heart. It intends to represent a comprehensive view on the causes and developmental processes in congenital heart disease. To be useful to the clinician and radiologist such a representation has to be simpler than the extremely complicated theories in the literature. The present study is based on a genetical basis which is more fundamental than the morphological basis of previous theories. Such a genetical basis is more suited to elucidate the main lines in the complicated processes in the development of the heart.

HARRIS and FARBER 1939 represent the controversial theories of the transposition of the large vessels, a malformation which is essential to the understanding of the causes and developmental processes in the normal and malformed heart. These authors also deal briefly with the relationship between transposition and visceral inversion. The latter anomaly is also essential to a comprehension of the development of the heart and the causative factors involved. TORGERSEN (1939) has dealt with the genic factors in the asymmetry of the viscera.

These problems are hardly soluble on a comparative anatomical, embryological or teratological basis. It is an hazardious task to draw conclusions from the morphology of the heart in other vertebrates concerning the normal and pathological development of the human heart. It is equally questionable to base theories on transposition on indirect inference from the normal development of the heart. No one has had

[1] Submitted for publication, Oct. 21, 1949.

at disposal a series of embryos showing the early stages of this malformation. Most authors base their opinion on museum specimens of the heart, not infrequently on a few cases. This procedure is dubious considering the fact that the heart is a part of the vascular bed and the organism. A comprehensive view on the development of the heart presumes a study of the heart and its relationship to the vascular bed and the whole organism. It has to be based on a genetical, embryological and clinical basis.

A study of the literature shows that it is hardly possible to separate the morphological and causative aspects of the problem. Equally artificial is a strict classification of the causative factors as purely genetical, purely haemodynamic, or even as purely infectious.

According to the opinion of the author acquaintance with the studies of PERNKOPF on the morphology of partial inversions 1926 and 1928 is indispensable to a comprehension of the development of the heart and the mode of action of the genetic factors involved. In 1935 PERNKOPF and WIRTINGER came to the conclusion that the pathological development of the heart in transposition is a part of the problem of the development of visceral asymmetry. In 1937 PERNKOPF made an observation suggesting the genetical relationship between partial and complete situs inversus. The present study did not start from these basic morphological studies of PERNKOPF. The morphological approach to the problem is confirmed by the genetical approach.

According to the opinion of the author the controversies concerning transposition are partly due to the use of ambiguous terms. The term inversion means the mirror image of the normal asymmetry, transposition means a displacement of an organ or a part of an organ beyond the midline. It is hardly possible to state whether an anomaly represents a transposition or an inversion in many cases. One has to consider that an organ may be inverted with regard to topography or with regard to structure. In many cases one has to deal with a mingling of transposition and inversion. The strict separation of transposition and situs inversus as emphasized by SPITZER is a theoretical construction.

The overriding aorta is transposed according to this terminology. It may also be called dextroposed as in the publications of TAUSSIG (1947). This author reserves the term transposition to the cases of crossed transposition.

The term bulbus cordis presumes that this part of the heart tube is homologous with the bulbus cordis of the Elasmobranch heart. The term conus used by KRAMER (1942) is more neutral.

The illustrations in the last chapter are schematic. They are partly redrawn from illustrations in the publications of TAUSSIG, PERNKOPF and WIRTINGER and KRAMER.

Own Observations

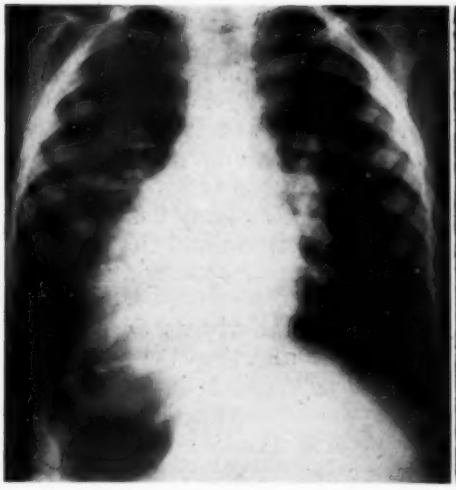
The data concerning the occurrence of heart defects in individuals with situs inversus and in the families of these individuals are represented in the paper of the author in the Archives of Pathology 1949.

The bearing of the observations concerning the developmental genetics of the heart had to be interpreted with some reserve. The high correlation between situs inversus and heart defects clearly demonstrates the relationship between the asymmetry of the viscera and the developmental of the heart. The data were not convincing concerning a genetical relationship.

The data indicated that the asymmetry of the viscera depends on the integrative action of complexes of genes affecting the particular organs. This observation confirm PERNKOPF's conclusions from the morphological data that the asymmetry of the organs depend on growth differentials inherent in the particular organs. The organs may show a relative independence concerning visceral asymmetry. It had to be expected therefore that the cases of situs inversus combined with heart defects constituted a particular group from a genetical point of view.

The investigations of the author of the genetics of visceral inversion have been going on for seven years. After the publication of the paper concerning the genic factors in asymmetry, the supposition of a genetical relationship between situs inversus and congenital defect has been confirmed in a conclusive way. The family is briefly mentioned in the paper referred to. The data represented in the present paper are obtained by a supplemental investigation after the recent birth of a child showing a congenital heart disease. In a way this conclusive observation is a parallel to the observation of PERNKOPF (1937) concerning the same problem after years of intensive morphological studies.

A boy, three years of age, showed situs inversus and clinical and radiological symptoms of a malformation of the heart (fig. 1). The boy is slightly cyanotic and shows the characteristic infantilism seen in many cases of congenital heart disease. He suffers from rather severe dyspnoea while playing. The parents had been married for 7 years when the boy was born. The mother had had two previous abortions, certainly involuntary. Three years after the birth of the child with congenital heart disease and situs inversus, the mother gave birth to a child showing congenital heart disease of the cyanotic type. The child died two months of age (fig. 2). Both these children have been examined at the university clinic. A maternal cousin of the mother showed cyanosis and infantilism. He was examined at the university clinic several years ago and demonstrated at a conference as a characteristic case of congenital heart disease. The roentgenogram is discarded but according



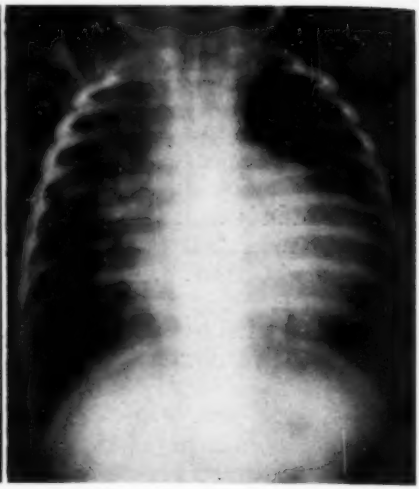


Fig. 1. Fig. 2.

Fig. 1. Boy showing situs inversus and clinical and radiological signs of a congenital heart defect.

Fig. 2. The brother of the boy with situs inversus and a congenital heart defect. He showed an enlarged heart and clinical and radiological evidence of a congenital heart disease.

to the hospital record the heart was enlarged and in the normal situs. The child died 14 years of age. The mother of this boy told that one of her sisters had had exactly the same symptoms as her son. She showed a high degree of cyanosis and retarded development and died about the same age.

It might safely be excluded that this occurrence of congenital heart disease in two brothers and a first cousin and an aunt of the mother is due to chance (fig. 3). The observation shows an effect of the genes. A recessive mechanism is probable. However, an incomplete dominance can not be excluded. The fact that the mother during ten years of marriage has two abortions and gives birth to two children showing congenital heart disease indicates

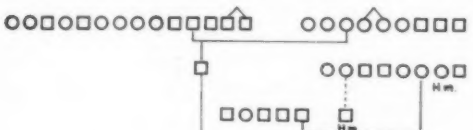


Fig. 3. Pedigree. S. i. — situs inversus, H. m. — heart malformation.

Fig. 4.

Fig. 5.

Fig. 4. Situs inversus of the liver, normal situs of the heart and probably a right aortic arch.

Fig. 5. Normal situs of the liver, situs inversus of the heart and a left aortic arch. The two pictures are mirror images and demonstrate the integrative action of the factors in visceral asymmetry in the development of the heart. Both children show a congenital heart disease of the cyanotic type.

that the genic factors manifesting themselves as a malformation of the heart and a situs inversus in other cases may manifest themselves as abortions. If this is the case four affected in four pregnancies is surprising presupposing homozygosity concerning a single gene as the cause of situs inversus and congenital heart defect in this family. This ratio of affected to normal may be due to chance but it is more probable that the genic factors involved is not a single recessive gene. No abnormalities have been detected in the family of the father. The family lives in a part of the country which has been examined by mass roentgen and no case of situs inversus has been detected in the family which is very prolific. There are, however, some peculiarities in the pedigree. One of the paternal great grandmothers was one of a pair of probably dizygotic twins. She gave herself birth to a pair of probably dizygotic twins. Among the maternal uncles and aunts of the father is a pair of probably monozygotic twins. In the family of the father three twinbirths occurred in 44 births in three generations. No twinbirth occurred in 44 births in the family of the mother.

The high frequency of twinbirths in the family of the father may either be due to chance or to factors in the genotype conditioning the manifestation of the abnormal gene in the genotype of the mother. The data in the study of the author (1949) are good evidence that the genic

factors in twinning are responsible for a particular group of cases of situs inversus.

Another remarkable peculiarity in the pedigree is the decrease in fertility. Previous generations being very prolific, the father of the child with situs inversus is the only child, the mother belonging to a sibship of two. There is no reason to assume that the decrease in fertility has social reasons. It is probable that it has a relationship to the factors which are at the basis of the abortions and malformed children in this family.

The occurrence of congenital heart defect in a collateral line excludes the possibility that the association of visceral inversion and congenital heart disease is due to environmental factors. Considering the clinical experience that environmental factors affecting the embryo is important in congenital heart disease the observation of the association of congenital heart disease and inversion in siblings is not conclusive concerning the effect of the genes.

Comments

PERNKOPF's observation 1937 concerned a child showing multiple congenital defects, among them partial inversion and transposition of the large vessels. The father showed a complete situs inversus. This case demonstrates the genetical relationship between transposition and visceral inversion. According to GÄNNSLEN, LAMPRECHT and WERNER (1940) a third and a fourth case have been observed by BAUMGARTH and ROESLER respectively. The first author observed a child with dextrocardia, transposition and stenosis of the pulmonary artery. Two maternal aunts had died of congenital heart disease. The second author reports the occurrence of dextrocardia, pulmonary stenosis, transposition and inversion of the ventricles in a child the brother of whom showed a congenital heart disease. The parents were first cousins.

The correlation between situs inversus and a variety of heart defects is evident. Even small inversions in the region of the liver and gallbladder and abnormalities with regard to the asymmetry of the venous backflow may be associated with a defective development of the heart. The correlation between inversion and transposition of the large vessels is obvious. An inversion may concern even single organs or even parts of an organ such as the liver, the intestine and particularly the heart. According to the interpretation in the study of the author 1949 it depends on the organ or part of the body affected by the genes whether an individual is going to show a complete situs inversus, partial inversion or a malformed heart. The genes affecting the parts of the body, the heart and the asymmetry of the viscera influence each other mutually,

the single genes affecting the development of the particular trait, the complexes of genes acting as modifiers.

Both malformation of the heart and situs inversus are correlated to a defective development of the lower jaw (GRUBER, 1920). HARRIS and FARBER report the observation of transposition and aortic coarctation in cleft palate and micrognathia. This fact shows the influence of factors affecting the development of the derivatives of the gill arches.

Heart defects, among them transposition (HARRIS and FARBER), as well as situs inversus occur in cases of harelip and cleft palate more frequently than expected if the combination was due to chance. This is particularly the case in gross malformations in which the effect of the genes is difficult to trace. In such malformations both the derivatives of the gill arches and the symmetry of the organism may be supposed to be affected primarily, cleft palate being in itself an expression of abnormal growth differentials in relationship to the midline.

The relationship to the derivatives of the gill arches is obvious in the high correlation between abnormalities of the aortic arches, heart defects and situs inversus. This correlation besides the abnormalities in the regions of the venous backflow is the basis of an understanding of the developmental processes in the malformation of the heart and the relationship of these malformations to visceral asymmetry. According to TAUSSIG anomalies of the spine are common in heart defects. This is also the case in situs inversus (TORGERSEN 1949).

TAUSSIG referring to STREETER interprets the association of abnormalities of the spine and heart defects as due to the stress and strain put upon the developing heart from the growing embryo. One has to consider that the position of the vessels depends on the topography of the embryo in the prevascular stage. The observations show that the factors in metamerism and bilateral symmetry are of particular importance.

PERNKOPF and WIRTINGER (1935) come on a morphological basis to the conclusion that transposition of the large vessels is due to an abnormal symmetry of the bulbus-truncus septum.

It is surprising to state that SPITZER (1929) and DOERR (1938) maintain that transposition and inversion are of a different »Wesen». The term »Wesen» or quintessence is hardly possible to define. Whatever may be the quintessence of transposition and inversion and the varying definitions of these terms, it is a fact that they depend on the same causes and may be conceived of as closely related processes also morphologically. The complicated representation of PERNKOPF and WIRTINGER (1933) concerning the processes taking place in the partitioning of the arterial trunc is in conformity with the representation of KRAMER (1942). Probably the disagreement among the authors concerning the developmental processes in transposition is partly due to an underestimating of the

importance of the fact that the partitioning takes place over the right ventricle (fig. 6). Transposition of the aorta is a normal occurrence in ontogeny, or to speak in the terminology of SPITZER, a functional right-chambered aorta is a transitional stage in individual development. Abnormal growth differentials of the truncus-conus ridges and the epimyocardial layer may produce a crossed transposition, an overriding aorta and a pulmonary stenosis. These abnormal growth differentials express themselves partly in a disturbance of the morphogenetic process displacing the arterial trunc towards the left, partly in an abnormal direction of the twisting of the truncus-conus ridges. Due to the part played by the conus ridges in the formation of the ventricular septum these abnormalities are often associated with defects of the ventricular septum. The tetralogy of FALLOT represents a persistent but distorted embryonic form. A crossed transposition is a manifestation of an inversion of these growth differentials, often associated with inversion in other parts of the heart. DOERR rejects the theory of PERNKOPF and WIRTINGER concerning the rôle of the bulbar ridges in transposition on the basis that a transposition may occur in cases without any bulbar ridges. It is difficult to see why a transposition can not be the result of an inversion of the direction of the relative growth of the layers of the wall of the arterial trunc and of the truncus ridges towards the ventricles.

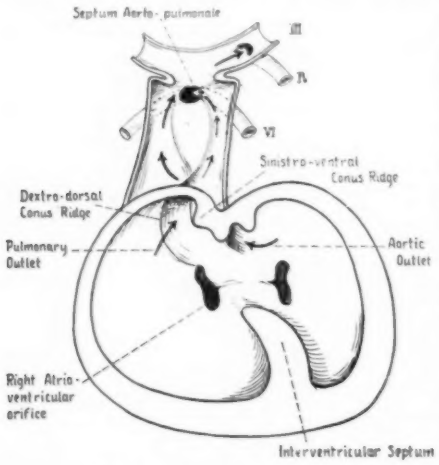


Fig. 6. Schematic drawing intending to show the partitioning of the arterial trunc over the right ventricle and the relationship of the ridges between the aortic arches to the truncus-conus ridges.

Transposition and inversion are both correlated to a variety of abnormalities of the heart and the aortic arches. The correlation of transposition to tricuspid and mitral atresia may be due to the associated disturbance of the growth of the atrioventricular cushions. However, in many cases the endocarditis in the malformed heart or haemodynamic factors may aggravate the malformations caused by the genetic factors. Asymmetrical growth expressing itself in hypoplasia of the right antimere of the heart as in tricuspid atresia may also affect the conus ridges producing pulmonary stenosis and transposition (fig. 7). The trans-

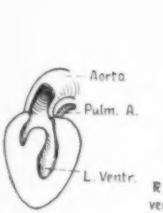


Fig. 7.

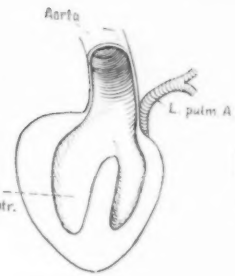


Fig. 8.

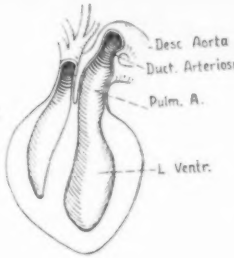


Fig. 9.

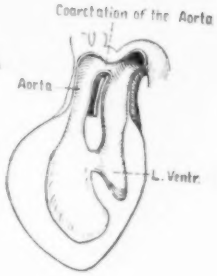


Fig. 10.

Fig. 7. Defective development of the right ventricle combined with extreme dextroposition of the aorta and pulmonary atresia (After TAUSSIG 1947).

Fig. 8. Tetralogy of FALLOT with a right aortic arch (After TAUSSIG 1947).

Fig. 9. Transposition of the great vessels combined with complete interruption of the isthmus of the aorta (After TAUSSIG 1947).

Fig. 10. Transposition of the great vessels, defect in the ventricular septum, coarctation of the aorta of the infantile type (After TAUSSIG 1947).

position in hypoplasia of the right ventricle is an example of a transposition caused by asymmetrical growth in the heart itself. Abnormal asymmetrical growth rates in the atrial region in cases of transposition may displace both auricles to the left of the aortic trunc, BREDT (1937). In the ventricles such asymmetrical growth rates may cause an inversion, in the arterial trunc distorsion and abnormal twisting of the septum. The topography of the metameres are distorted in the pericardial cavity, the relationship between the layers in the arterial trunc which is relatively fixed due to the connexion with the branchial mesoderm and the aortic arches. Also the muscular structure of the heart is influenced by these morphogenetic movements as demonstrated by PERNKOPF (1926) concerning the structure of the cortex in partial inversion of the heart.

Transposition is seen in a right aortic arch (fig. 8) and in individuals in which the right subclavian artery is the last branch of the aorta. Transposition is further seen in cases of interruption of the aortic arch at the isthmus (fig. 9) and in cases of coarctation of the infantile type (fig. 10). These associated anomalies of the vessels of the gill arches are particularly illustrating concerning the causes and morphogenesis of transposition. Abnormalities of the primordia of these regions caused by abnormal growth differentials in symmetry and metamerism cause an abnormal position of the vessels. These grow towards the heart dissecting the ventral aorta externally by the growth of the epimyocardium,

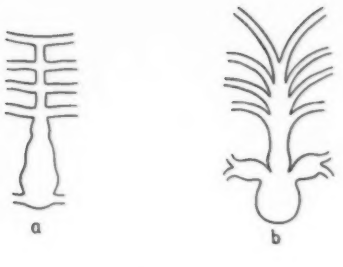


Fig. 11. The heart and aortic arches a. in fish, b. in amphibia and c. in reptilia. The influence of the transformation of the metameres and the gill arches on the direction of growth of the ridges between the aortic arches is evident by a comparison of a. and b. The relationship between these ridges and the partitioning of the arterial trunc and the heart will be seen by a comparison of b. and c.

internally by means of the subendothelial tissue of the truncus ridges. This tissue, the cardiac jelly, is according to BARRY (1948) essential also to the haemodynamics of the embryonic heart. The ridges between the arches grow towards the heart presumably influenced by the blood-stream. If the right aortic arch is going to persist and if the ridge on the right side is going to be the main constituent of the septum the direction of growth of the conus ridges is influenced by the asymmetry reversal of the blood-stream. The aorta tends to be transposed.

The influence of the vessels of the gill arches is evident also in phylogeny demonstrating the correctness of the view of SPITZER. The increasing asymmetry and the rearrangement of the metameres resulting from the transformation of the gill arches and the development of the lungs is seen by a comparison of the vascular anatomy of the fishes, the amphibia and the reptilia (fig. 11). The dissecting growth of the ridges between the vessels of the gill arches is apparently decisive to the development of the heart and the separation of the arterial and venous blood. The aortico-pulmonary septum in the reptilia is derived from the ridge between the fourth or sixth arches. The septum aorticum separating the right-chambered aorta from the truncus arteriosus is derived from the ridge between the third and the fourth arch on the left. The factors involved in the transformation of the gill arches in phylogeny and in the malformation of the heart are essentially the same. The malformed primordia of the derivates of the gill arches in ontogeny are replaced by the growth differentials of these organs in phylogeny. Considering the conformity of the species concerning the laws of heredity there is reason

to suppose that the same modifying factors have been at work in phylogeny as in the development of the normal and abnormal heart in ontogeny. The genetic factors in asymmetry have been fundamental in the evolution of the organs of respiration and the transition from gill respiration to lung respiration.

EKMAN (1924) has shown that the amphibian heart has a high power of self-differentiation. STÖHR JR. (1924) emphasizes the influence of the blood-stream and the correlative development of the neighbouring tissue. Mechanical terms in the description of the development of the heart have only a value as metaphores. The embryonic heart develops by self-differentiation according to the inherited growth differentials of the bilateral primordia of the heart, and by dependent differentiation due to the correlative development of the body and the vascular bed, and by functional differentiation due to the influence of the blood-stream. The developmental processes of the heart is a unity, the particular parts showing a varying degree of independence. The genetic factors in asymmetry behave as modifiers integrating the development of the parts.

The shape and organization of the heart may be supposed to be due to mutations and natural selection. The organs of locomotion and respiration may be regarded as expressions of a primary adaptation to the external environment, the morphology of the heart as a secondary internal response to the adaptive variations in the morphology of the body. The genes determine the development of the heart both as a self-differentiating organ and as an organ whose differentiation is dependent on the whole organism.

A transposition may be due to an abnormality of symmetry in the transformation of the aortic arches. On the other hand a right aortic arch may be assumed to persist in cases in which the right arch instead of the left is in the direction of the blood-stream due to a symmetry disturbance of the heart. The blood-stream may have a corresponding aggravating effect in defects of the septa. Considering the factors at work in the evolution of the heart the alternatives anlage or haemodynamics are not controversial. The morphology of the heart is a result of an adaptation of the heart to the function. Functional characters have been decisive in the selective processes concerning the genetic factors involved.

A great many cases of complete situs inversus may be determined before the establishment of the circulation. The inversion resulting from the rotation of a piece of the notochordal material (MEYER (1913)) may be due to inductive influences or to an indirect influence of changes in the region of the venous backflow. On the other hand the inversion taking place in the region of the gill arches in these experiments suggests the intimate connexion of the development of the asymmetry of the heart and the gill arches. An effect of inductive influences from

the notochordal field can not be excluded. The anomalies of the spine in visceral inversion and heart defect may be an expression of such primary disturbances of the notochordal field. This suggestion is not incompatible with the assumption that the anomalies of the spine are expressions of abnormalities of the metameres influencing the position of the primitive vessels. The inductive influence in the early stages may be assumed to take place by diffusion in the same way as the nutrition. The growth stimulating function and the nutritional function are both in later stages mediated by the vascular system.

By splitting the heart rudiment into two parts COPENHAVER (1926) produced two hearts, the right invariably showing situs inversus. (Fig. 12.) Abnormalities as transposition and isolated inversion may depend on the stage and place in which the causative factors unfold their effect on the bilateral primordia of the heart. The genetic factors in asymmetry are at work in the development of the bilateral primordia of the heart as well as in the development of the primordia of the regions in which the vessels are going to develop. Both developmental processes influence each other mutually by the integrative action of the genic factors in visceral symmetry and in later stages by haemodynamic factors. It is hardly justified to consider the stage of manifest differentiation of the heart and vessels as the most important in development. The abnormal development may be determined before the differentiation of the heart and vessels has taken place.

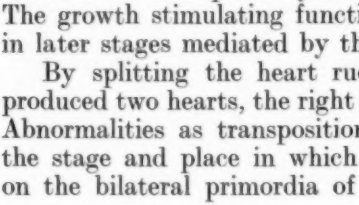


Fig. 12. Illustrates the potentialities of the two halves of the heart as demonstrated in the splitting experiment.

The defects of the septa in arachnodactyly and in mongolism show the relationship between abnormal growth of the body and a maldevelopment of the heart. Arachnodactyly is an example of genic factors influencing the development of the heart as a secondary effect. The relatively frequent occurrence of supernumerary nipples in children with congenital heart disease (BROWN (1939)) demonstrates the relationship between sexual differentiation and the development of the heart. The fact that transposition and related anomalies are more frequent in boys indicates the influence of the chromosomal balance in sex. The supposed mode of action of the chromosomal factors in sex shows a striking similarity to the mode of action of the hereditary factors in asymmetry suggested in this paper. The sex ratio in heart defects and in visceral asymmetry indicates an integration of the genetic factors in sex, symmetry and heart development. The extremes with regard to the alter-

natives of asymmetry is equally frequent in the sexes. The intergrades both regarding sexual differentiation and visceral asymmetry are more common in boys. This integration of the factors in sex and asymmetry may be assumed to be the cause of the sex ratio in heart defect and of the frequent occurrence of supernumerary nipples in these children.

The frequency of consanguineous marriages of all degrees in 97 cases of heart defect is according to GÄNNSLEN, LAMPRECHT and WERNER (1940) 6 per cent against 2 per cent in the population. The many reports of familial occurrence of particular defects such as patent ductus arteriosus and coarctation of the aorta (TAUSSIG, WALKER and ELLIS (1940), WALKER (1934), STEIN and BARBER (1945)) show the effect of genes affecting the primordia of the parts in which the vessels are going to develop. The defects behave in some cases as dominant traits, in other cases as recessive traits. The most reasonable interpretation of the observations is that the manifestation of the main genetic factors depend on the homozygosity concerning modifiers, among them the modifiers in the asymmetry of the viscera.

The effect of environmental factors is probable in virus infection though their mode of action in these cases still is obscure. These children tend to show phenocopies of the malformations observed in congenital heart disease generally. Of particular interest are the experiments of SAWIN 1948 concerning the inheritance of the variation of the spine and of WARKANY and WILSON 1948 concerning the influence of the nutrition of the mother on the variations of the aortic arches. Hereditary and nutritional factors were shown to influence the variations and asymmetry of the spine, ribs and the aortic arches. In vitamin A deficiency the last authors observed a right aortic arch, a double aortic arch or the right subclavian artery originating from the descending aorta. How often the genes and how often the environment are responsible for a congenital heart disease is hardly possible to estimate. Probably both factors are responsible in many cases, malnutrition, infections or endocrine and metabolic disturbances in the mother causing malformations of the heart in embryos with particular inherited potentialities. In adults even functionally unimportant anomalies cause a predisposition to endocarditis. The genes and the environment produce identical effects because both influence growth differentials which are essential to the position of the vessels.

The heart shows asymmetries which are essential to the separation of the arterial and venous blood and has to adjust itself to a symmetrical organism. The topography, shape and structure of the heart is a result of the suppression of bilateral symmetries in the heart itself and in the primordia of the vascular bed. The developmental processes caused by the genetic factors favouring one alternative concerning asymmetry may be

supposed to take place at a higher speed suppressing the other alternative. Their mode of action may be assumed to be parallel to the supposed mode of action of the genic balance in sexual differentiation, one alternative developing faster, the other alternative being suppressed.

A heart defect may be conceived of as a manifestation of an abnormality of asymmetry, caused either by the genes or by the environment. This disturbance of asymmetry may either manifest itself as gross malformation or as extremes or intergrades concerning the alternatives with regard to visceral asymmetry. This apprehension of the cause and the developmental processes in the malformation of the heart may be useful to the clinician and the radiologist. It is important to know why these patients show particular combinations of anomalies and constitutional peculiarities, which combinations of anomalies are to be expected in the particular case, and which of them are due to the primary cause of the disease and which are secondary to the circulatory insufficiency.

SUMMARY

There is a correlation between situs inversus, transposition and other congenital heart defects. The observation of situs inversus, with or without heart defect, in one member of a family, and of transposition or other heart defects in other members may be regarded as conclusive evidence that the genetic factors in visceral asymmetry and in the development of the heart influence each other mutually. The region affected primarily by the genetic factors in heart defects may vary. They act as a part of the genesit complex in visceral asymmetry which may integrate the development of the different parts of the viscera.

ZUSAMMENFASSUNG

Es besteht eine Korrelation zwischen Situs inversus viscerum, Transposition und anderen Missbildungen des Herzens. Das Vorkommen von Situs inversus, mit oder ohne Missbildungen des Herzens, bei einem Mitgliede einer Familie, und von Transposition oder anderen Missbildungen des Herzens bei anderen Mitgliedern, ist ein Beweis dafür, dass die Erbfaktoren, die für die viscerale Asymmetrie und für die Entwicklung des Herzens bestimmend sind, einen Einfluss auf einander ausüben. Die Region, welche die Erbfaktoren primär angreifen, ist verschieden. Diese Faktoren wirken als ein Komponent des Komplexes von Erbfaktoren, welches für die viscerale Asymmetrie verantwortlich ist und die Entwicklung der einzelnen Teile der Eingeweide und des Herzens integriert.

RÉSUMÉ

Il y a une correlation entre site inverse, transposition et les autres lésions congenitales du cœur. La constatation d'un site inverse, avec ou sans lésion du cœur, chez l'un des membres d'une famille, d'une transposition ou d'une autre lésion du cœur chez les autres membres, peut être considérée comme évidence conclusive, que les facteurs génétiques déterminant et l'asymétrie viscérale et le developpement du cœur ont une influence mutuelle les uns sur les autres. La région affectée la première par les facteurs généti-

ques dans les lésions du cœur, peut varier. Ces facteurs font partie du complexe génétique qui est responsable de l'asymétrie viscérale et lequel doit probablement intégrer le developpement des parties differentes des viscères.

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FROM THE ROENTGEN DIAGNOSTIC DEPARTMENT OF KAROLINSKA SJUKHUSET, STOCKHOLM, SWEDEN (HEAD: PROFESSOR ÅKE ÅKERLUND).

INTRAMURAL SMALL-CYSTIC DIVERTICULOSIS OF THE GALLBLADDER[1]

by

Åke Åkerlund and *Ulf Rudhe*

Normal and Pathological Anatomy

Ever since the latter half of the 17th century, gland-like many-branched outpouchings of the gallbladder mucosa within its wall and communicating with the lumen of the gallbladder have been observed and described. As early as 1666, MALPIGHI in his »De viscerum structura exercitatio anatomica» mentioned such miliary formations in the wall of the gallbladder in the sheep and pig and named them glands. At the end of the 17th century RUYSCH described and illustrated such »glands» spread over the entire wall of the gallbladder of the ox, pig and man, although he found them to be less numerous, smaller and more difficult to show in the last-mentioned.

In his »Handbuch der speziellen pathologischen Anatomie» (1842) VON ROKITANSKY described these formations as hernia-like outpouchings of the gallbladder mucosa. He also stressed that they could at times contain small concretions. Approximately 20 years later, he gave a somewhat more detailed description of these observations in his »Lehrbuch der pathologischen Anatomie». He stated that the hernia-like outpouchings of the mucosa in the gallbladder wall, which are sometimes very numerous and usually very small (of the size of a millet or hamp seed) commonly have very narrow openings. The dark-coloured concretions so often found in these formations therefore appear to be situated between the layers of the gallbladder wall.

Despite VON ROKITANSKY's description of these formations as minimal intramural hernias of the mucosa, they were stated by LUSCHKA, both

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in 1858 and 1863, to be definite glandular formations. He pointed out (Fig. 1) the considerable individual variations in the number and size of the »glands», from a few more or less plentifully branched up to fifteen or more, scattered over the whole area of the gallbladder and containing desquamated cells, detritus, bile pigment and fatty particles.

Ever since LUSCHKA's description, these lacunar outgrowths have been known in the German literature as »Luschkas Gänge» (ducts) or as »Luschka's crypts». This is so even since it has become apparent that they are not true glands but slit-like, often deeply branched invaginations or hernias of the gallbladder epithelium in the deeper layers of the wall. In the American literature they have long been known as Rokitansky-Aschoff's sinuses.

Fig. 1. »Gland» from the gallbladder wall of a Negro. 150 ×. (From LUSCHKA 1863.)

ASCHOFF made a thorough study of these formations in connexion with his well-known investigations of the origin of aseptic cholesterol concretions in gallbladder retention. The mucosa of the gallbladder lacks muscles (muscularis mucosae). The underlying muscular layer (tunica muscularis) is somewhat wide-spaced and of irregular structure. Through some of the meshes in the muscular network the blood vessels penetrate. These spaces are often dilated in gallbladder retention. The mucosa herniates through them into deep, split-shaped, often richly branched outpouchings which can extend far into the tunica fibrosa. In their deeper parts they can be dilated cylindrically or in the manner of a cyst and thus show a picture in agreement with that of false diverticula. ASCHOFF showed, with convincing illustrations, that these diverticular formations — which he named Luschka's ducts or Luschka's diverticula — are of decisive importance for the origin of the aseptic retention concretions represented by the cholesterol stones of radiate structure. Two of ASCHOFF's fine pictures are reproduced here. One (Fig. 2) shows very dilated, intramural diverticula and the other (Fig. 3) intramural cholesterol concretions found in such deep diverticula.

In the American literature on the morphology of the gallbladder, HALPERT's studies of these outgrowths have attracted much attention. Among other facts, he showed that it is indubitably a question of acquired changes. They could not be found on serial section of 10 foetal gallbladders. HALPERT pointed out that Rokitansky-Aschoff's sinuses

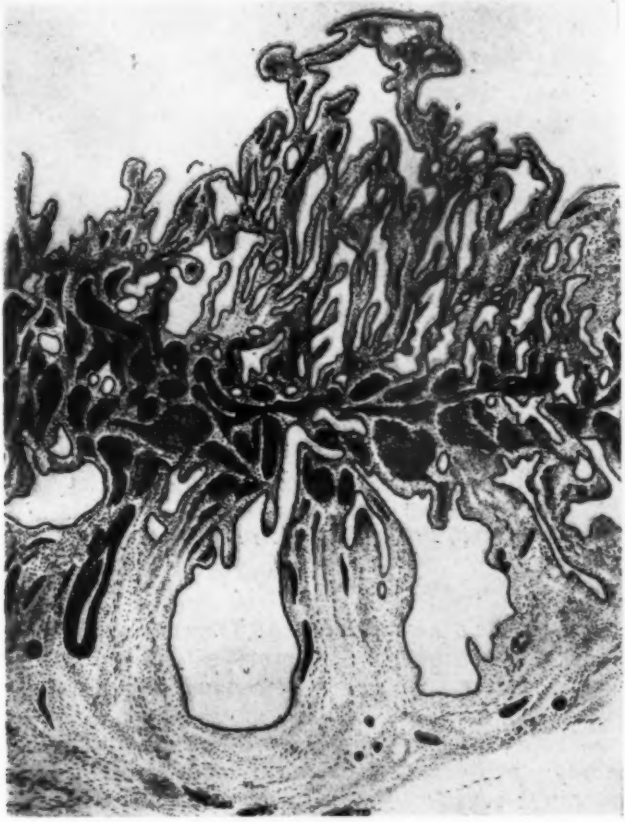

Fig. 2. Very dilated intramural diverticula which have penetrated the muscular layer and reach far down into the perimuscular connective tissue.
(From ASCHOFF & BACMEISTER 1909.)

are identical with the structures named »hernia-like outpouchings of the gallbladder mucosa» by VON ROKITANSKY in 1842, described as »Luschka's ducts» by ASCHOFF in 1905 and termed »Aschoff's ducts» by SHIKINAMI in 1908. Moreover, according to HALPERT, another kind of duct-like formation of the same histological appearance and structure as the intrahepatic biliary ducts is not infrequently found in the periphery of the gallbladder wall, particularly where it lies against the hepatic surface. These formations do not, however, communicate with the lumen of the gallbladder. As they were described by LUSCHKA as early as 1863, HAL-

Fig. 3. Laminated cholesterol concretions in intramural gallbladder diverticula. (From ASCHOFF & BACMEISTER 1909.)

PERT named them »true Luschka ducts». They have no association with the aforementioned outpouchings or crypts of Luschka and the term suggested by HALPERT is therefore somewhat inappropriate and more likely to give rise to further confusion.

A few years ago, ROBERTSON and FERGUSON of the Mayo Clinic made a very thorough pathologico-anatomical study with an extremely exhaustive historical review of intramural gallbladder diverticula. They stressed the similarity in the structure of the intramural gallbladder crypts and diverticula in the small intestine, the colon and the urinary bladder. At the same time they pointed out the marked tendency of the gallbladder crypts to folding and branching. In this way they differ from all the other diverticula in the human body, a fact ascribed to the particular construction of the gallbladder wall. They suggested the term »gallbladder diverticula», which appears to be an adequate expression of the nature of the changes. They studied 495 gallbladders, of which 320 were extirpated surgically and 175 examined at autopsy. These formations were divided into three groups, according to the microscopical appearance: (1) when the diverticula reached the tunica muscularis; (2) when the diverticula were found in the intermuscular lacunas; (3) when the diverticula penetrated the muscular layer into the underlying connective tissue and possibly even to the serosa.

They found that the anatomically normal gallbladders contained few diverticula and that they were then usually located superficially, only in the subepithelium. On the other hand, in the gallbladders extirpated at operation, the diverticula were so common that they were lacking only in 23 cases (7 per cent). In the operated cases the diverticula were not only more numerous but also appreciably deeper and more developed than in the normal gallbladders. An increase in the number of diverticula was found with increasing age. Briefly, they found that *in approximately 50 per cent of all the gallbladders of persons over the age of 30 there were herniations of the mucosa into the underlying layer of the wall, at times reaching as far as to the peritoneal margin.*

Fig. 4. Anatomical specimen of human vesicula (D), ampulla (C) and adjacent part of the ductus deferens (A) after injection of an opaque medium (B = ureter).

Numerous small-sized, narrow-necked, intramural diverticula of the ampulla and ductus deferens are visualized. 2 ×.

The diverticula may contain bile, bile pigment, cholesterol crystals and at times typical biliary concretions. Inflammatory changes are sometimes present but are often lacking altogether. Increased pressure in the gallbladder presumably plays an etiological rôle in the initial changes. The further development of the diverticula is due to the deficient functional adaptation of the gallbladder mucosa to a subsequent abnormal distension of the gallbladder with its accompanying abnormal process of stretching in its walls. All transitions exist between purely microscopical gallbladder diverticula and gross dilated such and between these various intramural forms of diverticulosis and large, bladder-shaped, solitary, plurilocal or multilocal diverticula that may deform the exterior of the gallbladder.

Fig. 5 a. MARCH's case 1948.

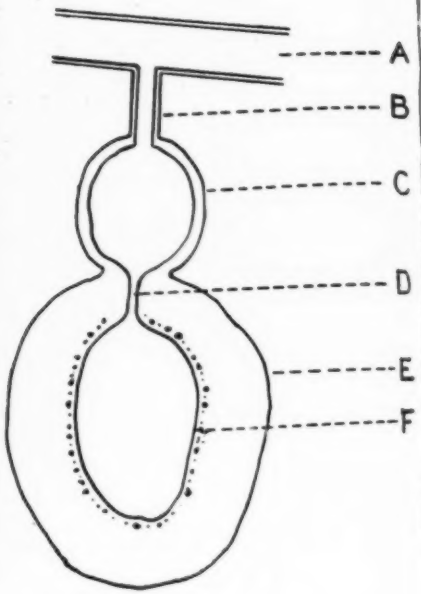

Fig. 5 b. A schematic drawing in longitudinal section of the operative and gross pathological findings.

A, common duct; B, cystic duct; C, upper pouch of gallbladder; D, stricture of gallbladder; E, greatly thickened lower pouch of gallbladder; F, bile-stained row of Rokitansky-Aschoff sinuses. (From MARCH, Am. J. Roentg. 59: 198: 1948.)

The question whether any definite congenital, »true» gallbladder diverticula exist must be left open. In any event, they must be extremely uncommon.

Small-cystic intramural gallbladder diverticulosis has an anatomical analogue in the physiological diverticula of the ampulla and the adjacent part of the ductus deferens. These structures also lack musculature in the mucosa. The narrow-necked diverticula stand out clearly in the figure (Fig. 4).

Roentgen Findings

Roentgenograms of solitary, acquired gallbladder diverticula have been described earlier by CHIRAY and LOMON (1934) among others and will not therefore be described in more detail here.

Fig. 6. ACKERMANN's case. Numerous diverticula around the lumen of the gallbladder. (From ACKERMANN Am. J. Roentg. 60: 258: 1948.)

Intramural gallbladder diverticulosis does not appear to have been the object of radiological study with the exception of one case reported by MARCH and another by ACKERMANN, both in the Amer. Journal of Roentgenology 1948.

In MARCH's case (Fig. 5 a and b) cholecystography showed a two-chambered, hourglass gallbladder containing contrast filling of a somewhat decreased degree of concentration. A thin, marginal, concentric layer of contrast which appeared to undermine the mucosa was seen around the lower pouch. This layer appeared more distinctly after a fatty meal. Pathologico-anatomical examination revealed that the gallbladder was partially divided into two sections by a stricture with a lumen no wider than a thread. Microscopical examination revealed long crypts in the wall of the lower pouch. These branched out as far as into the perimuscular connective tissue in the form of mucosal hernias and contained bile. Their distribution corresponded to the marginal concentric layer of contrast seen on the radiogram. No concretions were found in the gallbladder.

In ACKERMANN's case (Fig. 6) cholecystography showed contrast filling of a gallbladder of normal size and a good concentration of the contrast medium. Numerous, contrast-filled small-cystic diverticula were visible concentrically around the lumen. They became extremely distended after a fatty meal. A single gallbladder concretion was found. Operation was not performed.

We have found no additional cases in the literature.

Our Roentgen Observations

We had a similar case to the aforementioned at Karolinska Sjukhuset in the autumn of 1948. It afforded fresh views on the pathogenesis of biliary calculi and was thus not merely of interest as a case-history. We therefore consider a more detailed description warranted even though operative control is lacking.

Case-history. A fairly corpulent woman, aged 52. For the past 4—5 years discomforts in the epigastrium in the form of attacks of grinding pain, sometimes accompanied by nausea. The pain was usually felt deep down and radiated caudally to the right side of the abdomen. In between, hunger pain before meals. No sour eructations. Could not tolerate fat food and raw fruit. No icterus. No fever in connexion with the attacks of pain.

Examination. Abdomen: fairly fat. Considerable tenderness on palpation within an area of approximately a hand's breadth around the umbilicus. No muscular defense. No resistence palpable.

Urine: N. A. D. Stools: Weber test negative.

21. 9. 1948. *Cholecystography* (by mouth): no contrast filling of the gallbladder at the first examination. No calcifications or visible concretions at the site of the gallbladder. *Renewed cholecystography* on 23. 9. (Fig. 7) showed contrast filling of a somewhat small gallbladder. Good concentration of the contrast medium. A layer of contrast with a maximum thickness of one millimetre was seen concentrically in the gallbladder wall scarcely one millimetre from the lumen. It was most distinct at the fundus. Within the body and bordering on the cystic duct the layer of contrast was not continuous but had breaks of varying length.

The changes were seen both in the recumbent and erect position (Fig. 8). The lumen of the neck of the gallbladder was strikingly small and the cystic duct wide. After partial emptying on the following day, the gallbladder was approximately half its former size. Despite good density of the contrast in the gallbladder, the diverticula were scarcely discernible.

There was better contrast filling of the marginal layer on both occasions after an egg meal (Fig. 9). Slow emptying of the gallbladder.

On *renewed cholecystography* on the 28. 9., 2 cg of morphine were given subcutaneously one hour after the egg meal. The layer of contrast then appeared more distinctly and was better filled than earlier (Fig. 10). Serial films after 8 drops of nitroglycerin sublingually 45 min. later showed no change. No concretions were visible.

The patient's typical discomforts were accentuated in connexion with the egg meal and morphine injection. Nitroglycerin sublingually gave no relief. The patient refused to undergo operation.

The entirely similar findings in our case and in those of MARCH and ACKERMANN, although no pathologico-anatomical examination could be made in ours, should suffice to confirm the diagnosis of *intramural small-cystic diverticulosis of the gallbladder with a moderate degree of disturbance in the emptying of the gallbladder.*

It was not possible to establish whether the narrow lumen of the neck of the gallbladder was a contributory cause to this disturbance in emptying.

Fig. 7.

Fig. 8.

Fig. 7. The authors' case. A concentric, intramural layer of contrast, approx. 1 mm deep around the lumen of the gallbladder. The layer, comprised of a large number of contrast-filled diverticula, is most distinct at the fundus; it is not continuous in the body or on the borderline of the cystic duct.

Fig. 8. The same gallbladder, erect position.

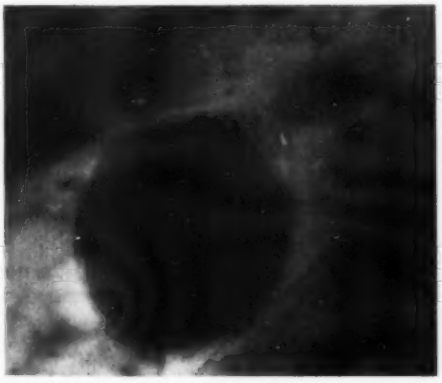

Fig. 9. After an egg meal.

Fig. 10. After an egg meal and 2 cg of morphine subcutaneously.

The marginal layer of contrast visible on the radiogram is due to the summation of the contrast filling in the many closely-lying diverticula. As their lumens are narrow both in the subepithelium and within the tunica muscularis, the direct communication with the lumen of the gallbladder cannot be demonstrated with certainty on the radiogram but can only be discerned faintly in places on the most distinct films. The concentric layer of contrast therefore appears to be independent of the gallbladder lumen.

Discussion

As early as 1938, one of the writers (ÅKERLUND) discussed in detail the contributions of the cystographic study of the layer formation and sedimentation phenomena of the gallbladder to the question of the origin of the aseptic cholesterol stones of radiate structure. It was then pointed out that the purest cholesterol concretions in undried, vital condition have a specific gravity of 1,040. This is the same as that given as the upper borderline for the highly-concentrated native bile which forms the sediment in a normal gallbladder with a good ability of concentration and that does not mix with a fresh inflow of less concentrated bile. These observations have led ÅKERLUND to the conclusion that there are good reasons for assuming that such aseptic cholesterol stones are formed by the crystallization of cholesterol from the concentrated residual bile in the sediment. The sediment of cholesterol crystals can be regarded as an initial stage in the formation of concretions. The prerequisites are an unimpaired ability of concentration with coincident incomplete emptying of the gallbladder.

The various investigations made by KOMMERELL (1942) have later substantiated the correctness of this view. He was thus able to show that when small, fresh gallstones are present, the contrast filling of the gallbladder is markedly dense as an expression of a pathologically raised ability of concentration in the gallbladder.

KOMMERELL also pointed out that in gallbladders with a so-called Phrygian cap or »Fundusknickung» a predisposition for the formation of aseptic biliary concretions must be envisaged on the grounds of the impairment in emptying. This also applies to individuals with a long, loosely hanging gallbladder, in which the fundus occupies the lowest point even in the supine position.

As long as we are dealing with a gallbladder with an apparently normal ability of emptying, it is difficult — as KOMMERELL found — to conceive that one and the same portion of bile could be retained and concentrated for so long that a crystallization of cholesterol would finally occur. It is true that the most concentrated bile always sinks to the

deepest point of the gallbladder but this point varies with the position of the body. A concentrated sediment, which is not emptied when the body is upright, can therefore relatively easily be emptied in the supine position and often still more easily in a slight Trendelenburg position.

A concentrated sediment of residual bile may, for some reason, be prevented from being emptied in the normal way. It therefore remains for a sufficient length of time to be concentrated to the specific gravity of pure cholesterol. An important condition is then fulfilled for the crystallization of cholesterol without the necessity of taking into account the exact physical process.

Intramural gallbladder diverticulosis is, in the microscopical form, a very common occurrence in more or less severe, possibly only »subclinical» disturbances in emptying of the gallbladder. It therefore appears to us to be just such an extremely important m chanical factor. Independently of the position of the patient's body or of possible variations in the shape or position of the gallbladder, it tends to enforce a lengthy retention of the same deposit of highly concentrated residual bile even when the gallbladder motility appears to be otherwise unimpaired.

Thus, in conjunction with the sedimentation phenomenon, intramural diverticulosis provides an acceptable mechanical explanation of the origin of the aseptic retention concretions in the gallbladder, i. e. the laminated cholesterol stones of radiate structure.

The retention and poor emptying of the diverticula appeared distinctly on the radiograms in MARCH's and in ACKERMANN's cases. They were namely distended in the emptying phase revealing an increased amount of contrast. This fact was also noted in our case, although it was less marked. Morphine further increased the effect of the egg meal. It thus caused a temporary improvement in the contrast filling of the diverticula during the first part of the emptying phase.

It may scarcely appear premature to assume that a maximally concentrated deposit of residual bile, enclosed in the small pocket-shaped diverticula of the gallbladder, constitutes an important mechanical condition for the inception of the first stages of the aseptic retention concretions. On the other hand, several details of the etiological mechanism are not yet elucidated.

We are aware, from numerous observations, including those of VON ROKITANSKY and ASCHOFF, that small, laminated cholesterol stones of radiate structure are common in diverticula in the gallbladder wall. We also know that these small concretions can, during their intramural stage, attain such a size that they cannot pass whole through the unchanged narrow neck of the diverticula. A question that is as yet unanswered is the following. Are the aseptic retention concretions as a rule

formed in such diverticula in the wall and then secondarily penetrate into the gallbladder? Or, are they originally formed in the gallbladder itself and later, possibly at a very early stage, pass as a sediment into the diverticula? It is not inconceivable that both these possibilities may occur.

We can now consider why this relatively common intramural gallbladder diverticulosis is so extremely seldom visible radiologically.

In many cases this is certainly due to a lack of contrast filling in the gallbladder or to the fact that this has taken place with an unduly low concentration of the contrast medium.

In other cases the diverticula are too small, too few or too shallow to appear on the radiogram.

The content retained in the diverticula, their occlusion owing to oedema or other inflammatory changes in the wall as well as unduly narrow necks are further reasons for an insufficiant contrast filling.

The following conditions must be fulfilled if the diverticula are to be demonstrable radiologically *in vivo:*

1. The gallbladder must be well filled with contrast and the contrast density sufficient. Unfortunately, the ability to concentrate contrast is often impaired in disturbances in emptying of the gallbladder.

2. The diverticula must be sufficiently *large* and sufficiently *numerous* as well as sufficiently closely *packed* and *branched*.

3. The diverticula must not contain any appreciable amount of retained bile components such as mucus, detritus or concretions, which prevent contrast filling. Moreover, they must be sufficiently *wide-necked* and so located that they are *freely projected* on examination.

One of the characteristics of so-called *acute pneumocholecystitis* is a distension of the gallbladder mainly by *gas* formed in it. Particularly favourable conditions therefore appear to exist for the appearance of these intramural diverticula on direct films owing to their filling with gas. In no less than 7 of the 14 cases of this disease described and illustrated in the literature (Simon, Culver & Kline, McCorkle & Fong (Cases 2 and 3), Heifetz & Senturia (Case 2), Šváb, and Jemerin) a gas-filled, small-celled intramural wall layer is seen of exactly the same appearance as diverticulosis (Figs. 11 and 12).

It was found in these cases that the streak of gas must be located in the gallbladder wall and that it appears relatively early in the course of the disease. Notwithstanding, none of the aforementioned authors suggested the possibility that the gas could have penetrated into small, preformed intramural diverticula and distended them. Nor were intramural

Fig. 11. McCorkle and Fong's case. Gas-filled gallbladder. Intramural concentric layer of gas around the gallbladder lumen. (From McCorkle and Fong. Surgery 11: 851: 1942.)

diverticula mentioned in the pathologico-anatomical reports on the four patients operated on or autopsied. In the majority of these cases, however, the gallbladder wall was already more or less necrotic when operation was performed and was not therefore suitable for a detailed microscopical study.

Pathologico-anatomical verification is lacking. Nevertheless the radiograms shown of the 7 cases of acute pneumocholecystitis, with this characteristic marginal streak of gas, permit an assumption that gallbladder diverticula distended with gas were present. Roentgen-anatomical studies of gallbladder specimens filled with air under pressure after previous careful emptying of the gallbladder content could possibly settle the question definitely.

Conclusions

Intramural small-cystic diverticulosis in the gallbladder wall, intrinsically due to the lack of muscles in its mucosa and lack of submucosa, is a common pathologico-anatomical finding in impaired emptying of the gallbladder. Its microscopical initial stages can almost be considered as physiological in middle-aged and elderly persons.

Fig. 12. ŠVÁB's case. Gas filling of the gallbladder with a concentric layer of gas around the lumen, spreading far into the wall. (From ŠVÁB. Gastr.-enterol. Bohema. čis. 3, roč. II.: 81: 1948.)

Such diverticula have been given a multiplicity of names — »glands», »Gänge», »ducts», »crypts», »sinuses», most often combined with a proper name (MALPIGHI, RUYSCH, LUSCHKA, VON ROKITANSKY, ASCHOFF). They have often caused confusion with other structures in the gallbladder wall such as mucous glands and aberrant biliary ducts.

These intramural diverticula appear to be an essential feature in a number of pathological conditions such as cystic cholecystopathy, cystic cholecystitis, cholecystitis glandularis proliferans, adenoma, cystadenoma and adenomyoma of the gallbladder. Its many designations have also given rise to confusion. We therefore consider that the term small-cystic intramural diverticulosis is preferable to any other. It characterizes adequately the process in question, *i. e.* herniation or invagination of the mucosa in the deeper layers of the wall with secondary, peripheral, cystic dilatation.

All transitions are found from a few, shallow purely microscopical subepithelial diverticula of the mucosa to widespread, closely-spaced perimuscular such visible to the naked eye, plentifully branched and cystically dilated. There are also transitions between intramural diverticulosis and single or multiple larger diverticula that cause a bulging or bladder-shaped deformation of the free outer surface of the gallbladder.

Although intramural diverticulosis is a common pathologico-anatomical finding it is seldom demonstrable radiologically, in any event with

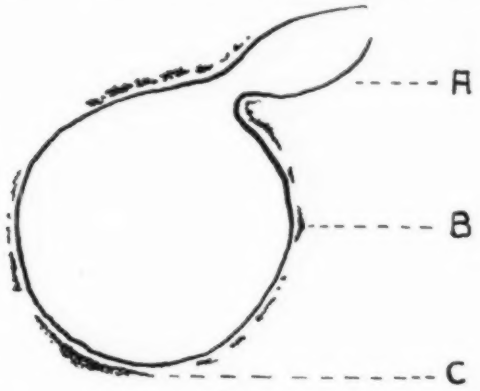

Fig. 13. Schematic drawing of the author's case.
A. the cystic duct and neck
B. intramural diverticula in the body of the gallbladder
C. corresponding formations in the fundus.

our present technique. The radiological finding made repeatedly in the same patient by us and completed by means of the two cases reported in the literature is entirely characteristic and pathognomonic for this affection.

This *typical radiological finding* (Fig. 13) consists of a more or less extensive and more or less continuous thin outline of contrast, closely following the shadow of the gallbladder and evidently located within its wall. This narrow marginal line of contrast, »corona» or border of contrast shows, at least in places, a suggestion of granulation or a columnar structure. In other places it is an even streak, reminiscent to some extent of the familiar radiograms in undermining of the mucosa of the alimentary canal. It is true that no distinct connexion is visible between this intramural layer of contrast and the lumen of the gallbladder. Nevertheless, it is possible with a loupe to surmise a few narrow connecting bridges on the most distinct original films.

The radiogram comprises a composite picture of numerous, contrast-filled, closely packed, plentifully branched and cystically dilated diverticula.

In addition to a good contrast density of the gallbladder shadow, the following conditions must be fulfilled if the changes are to be visible *in vivo* on the radiogram. The diverticula must be large enough, branched and cystically dilated. They must be sufficiently closely packed and wide-necked and freely projected. No retained bile components such as concentrated residual bile must prevent their contrast filling. It is obvious that these conditions are only fulfilled in exceptional cases.

We also consider it warranted to assume that intramural gallbladder diverticulosis was the cause of a small-cystic intramural streak of gas shown in some cases of the rare »acute pneumocholecystitis» in the literature, although none of the authors put forward such an interpretation.

Intramural gallbladder diverticulosis also provides a natural explanation of the following question brought up by KOMMERELL amongst others. Although there are variations in the position of the gallbladder and its ability of emptying is apparently unimpaired, one and the same portion of highly-concentrated residual bile can remain for a sufficient length of time for the first formation of the aseptic retention concretions, the cholesterol concretions of radiate structure, to be formed in the sediment. This is the purest type of the primarily formed biliary calculi in the gallbladder. The deep, branched, narrow-necked diverticula obviously present the best possible opportunities for the lengthy retention of the highly-concentrated sediment of the residual bile. Intramural diverticulosis of the gallbladder thus gives extremely strong support to the view on the etiological mechanism of aseptic retention concretions put forward by one of the writers (ÅKERLUND) in 1938. This was based on his cholecystographic studies of the layer formation and sedimentation phenomena in the gallbladder *in vivo*.

SUMMARY

An account is given of a *new roentgen finding, typical of intramural diverticulosis of the gallbladder*. This is based on the authors' observations in conjunction with two cases encountered in the literature. The finding consists of a more or less continuous, narrow streak of contrast, immediately adjacent to the shadow of the gallbladder and following it for varying distances. This contrast — »corona» — shows in places a suggestion of granulation or columnar structure. The radiological picture is due to the composite effect of contrast filling of a large number of closely packed intramural diverticula.

The origin, development and morphological nature of gallbladder diverticulosis are discussed against the background of the normal and morbid anatomy of the gallbladder wall. The prerequisites for the visualization of the condition are reviewed. It is pointed out that the rare »acute pneumocholecystitis» appears to afford special conditions for the direct visualization of the diverticula owing to their filling with gas.

The importance of diverticulosis of the gallbladder in the origin of the aseptic, cholesterol concretions of radiate structure in the retention gallbladder is stressed.

ZUSAMMENFASSUNG

Auf Grund eigener Beobachtungen, die zusammen mit einigen vereinzelten Mitteilungen aus der Literatur wiedergegeben werden, berichten die Verfasser über *einen neuen, für intramurale Divertikulose der Gallenblase typischen Röntgenbefund*. Dieser besteht in der Beobachtung eines schmalen, mehr oder weniger zusammenhängenden Kontraststreifens, der sich dicht neben und ausserhalb der Kontur der Gallenblase befindet und zu dieser auf gewisse Strecken einen Begleitschatten bildet. Stellenweise zeigt diese Kontrast — »Corona» — Andeutungen von Körnelung und von pallisadenförmiger Zeichnung. Dieses Röntgenbild entsteht durch die Summation der kontrastmittelgefüllten, in grosser Anzahl eng nebeneinanderstehenden intramuralen Divertikel. Es wird im Hinblick auf die normale und pathologische Anatomie der Gallenblasenwand über die Entstehung und Entwicklung, sowie über die morphologischen Eigenschaften der Divertikulose der Gallenblase berichtet. Auf die Voraussetzungen einer röntgenologischen Darstellung dieser Affektion wird hingewiesen. Hierbei wird auf die Beobachtung verwiesen, dass die seltene »Pneumocholecystitis acuta» wegen der Gasfüllung der Divertikel besondere Bedingungen für das Erscheinen der Divertikel im Röntgenbild aufzuweisen scheint. Die Bedeutung der intramuralen Divertikulose der Gallenblase für die Genese der aseptischen, radiär aufgebauten Cholesterinkonkrementen in Stauungsgallenblasen wird hervorgehoben.

RÉSUMÉ

En se basant sur des observations personnelles et sur quelques rares cas trouvés dans la littérature, les auteurs présentent *une nouvelle image radiologique typique pour la diverticulose intramurale de la vésicule biliaire*. L'image consiste en des traits de substance opaque plus ou moins continus, situés en dehors et tout près du contour de la vésicule biliaire qu'ils accompagnent sur une distance plus ou moins grande. Cette »couronne» opaque prend par place une forme granulée ou en palissade. L'image radiologique est produite par la somme d'un grand nombre de diverticules intramuraux serrés les uns contre les autres et remplis de substance opaque.

L'origine, le développement et les caractères morphologiques de la diverticulose de la vésicule biliaire sont étudiés en se basant sur l'anatomie normale et pathologique de la paroi de la vésicule biliaire. Les conditions pour la démonstration radiologique de l'affection sont exposées. Les auteurs signalent la rare »pneumocholécystite aiguë» qui semble offrir des conditions spéciales pour la visualisation sur le film direct des vésicules remplis de gaz.

Les auteurs insistent sur l'importance de la diverticulose intramurale dans la production de calculs cholestériniques aseptiques, à structure radiaire dans les vésicules biliaires stasiques.

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EXPERIENCES OF THE POLAROGRAPHIC SERUM PROTEIN REACTION IN CANCER DIAGNOSIS[1]

by

Arne Forssberg and *Sverker Nordlander*

General Principles

The polarographic serum protein reaction is based on an electrochemical procedure the details of which were mainly elaborated by BRDIČKA (1) (survey with many references). The method was originally claimed to be a cancer reaction. At an early date it was evident, however, that also inflammations, infections, bile and liver diseases and, generally, disorders accompanied with fever often gave a positive reaction. As far as we know, efforts to work out a differential diagnosis after fractionating the serum have failed. We are thus more right in speaking of a general test indicating, when positive, a pathologic state in about the same manner as does the sedimentation rate. This view has now been more or less generally accepted.

The polarographic method of analysis is thoroughly described in textbooks by f. i. HEYROVSKY (2) and KOLTHOFF (3). In order to discuss some details of the procedure in the following a short account of the principle must be given. In ordinary electrolytic analysis the voltage is kept at a constant value required for the separation of the substance under investigation. In the polarographic method, which is mainly used when analysing substances that can be electrochemically reduced, the voltage is continuously increased during the electrolysis. The reduction takes place at a dropping mercury electrode, the small mercury drops being of uniform size and falling at a constant rate through the test solution. At a defined voltage, increasing amounts of the substance are deposited and reduced on the surface of the drops. The resulting current is auto-

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matically recorded in a current-voltage diagram. The height of the curve is under appropriate experimental conditions a measure of the concentration of the substance.

The application of the method for serum analysis may be recapitulated as follows: BRDIČKA in 1933 (4) incidentally discovered that a solution of ammoniacal cobalt salts containing serum proteins, when polarographed caused a characteristic reduction »wave» at a defined voltage. As proteins alone or the cobalt do not show any reaction at the same voltage the effect must be caused by reduction of some primarily formed complex of cobalt and part of the proteins. Furthermore it turned out that only proteins and decomposed products from proteins containing sulphur in a disulphid or a sulphydryl bond show the effect. This view was supported by further investigations in which the polarographic results were compared with pure chemical determinations of the components mentioned, and by a polarography of cystin and cysteine, which yields curves of the same type.

We are here not concerned with a discussion of the theoretical aspects of the reaction but will present the methods used in clinical routine work. A great variety of methods exists (see f. i. 5—7) and the arguments for them and their advantages may, omitting quantitative details be put briefly as follows:

1) When investigating native sera, diagrams are obtained, which show on an average higher curves for cancer serum, as well as for sera from a great many other diseases, than for normal ones. The differences between normal and pathologic sera are, however, quite small with this method.

2) If the serum proteins are first denatured, f. i. by treatment with alkali or heat, the height of the curves increases, and by percentage more in normal sera, thus augmenting the differences mentioned above. The explanation seems to be, that part of the active groups which in the native serum are not free to react with the cobalt are now released through a partial disintegration of proteins. The percentage of liberated disulphid and sulphydryl groups is accordingly found to be greater in normal sera than in pathologic ones. The same results are obtained and the same explanation also holds good when the sera have undergone, previous to the polarography, a peptic protein fermentation.

3) Still another clinically used method and actually the most reliable one is based on the fact that precipitation of the serum proteins with sulphosalicylic acid from alkali- or heat-denatured serum gives a filtrate which shows the opposite effect, *i. e.* higher curves in pathologic sera than in normal ones. Instead of sulphosalicylic acid a number of other protein precipitating agents have been tried, f. i. alcohol. It is supposed that the sulphosalicylic acid dissolves some decomposition products of the proteins, which however still seem to be rather high molecular as they do not pass cellophane membranes.

We may add some general remarks. As far as one knows, the polarographic serum curves are caused by the same type of compounds from a chemical point of view, whether obtained from native serum or from samples first treated in any of the ways outlined above. The only differences between the various samples analysed is thus that we are con-

cerned in the special cases with more or fewer polarographically active groups in the solution resp. more or less inactive substances, among them a vast bulk of proteins which do not contain the S-linked components but may interfere in the reaction. Seeing now that the active components are absorbed on the surface of the mercury drop before the reduction takes place and that the other, inactive components in the solution may also be deposited on that surface, we may imagine, that a competition for the available space should complicate the quantitative judgement of the curves as the concentration of the participating components change. For clinical practice the only way seems to be an empirical search for procedures which give the most reliable differences between normal and pathologic sera.

The analyses carried out by most investigators are generally performed with some variation of the procedures described under 3). The curves obtained are either estimated in a relative scale, ranging from 0, indicating negative result (= »normal blood value»), to +++ indicating a strong positive reaction or, which is better from the reader's point of view, as a ratio between the unknown sample and the average normal value or the highest normal value taken from a reasonably big series of analyses on apparently healthy persons.

Fractionation of serum

Clearly the methods for fractionating the serum before the polarography could be varied almost infinitely. The implicit intentions should be to separate some fraction which would be more or less »specific» for cancer. As we pointed out above this prospect does not seem promising. It is conceivable, however, that a combination of a number of tests could give at least quantitatively sharper distinctions between »normal» and »pathologic» values. On that assumption, we tried a number of simple methods to separate the serum before the polarography. Afterwards we combined the tests in the way stated below. As this investigation only aims at what is possible to do in routine clinical work we have not tried any elaborate methods to fractionate the serum proteins. Of course combined methods as outlined below could be developed further. It is, however, impossible to foretell whether improvements which would make the work worth while could be gained.

The blood samples were taken in the morning or else as fasting values. The samples were left to coagulate for at least 2 hours and then the serum was centrifuged off. From a survey of various methods of fractionating the serum, either directly copied from other sources, or modified from general methods of protein precipitation, we selected and examined the following closer.

1 a) Following the procedure of BRDIČKA we denatured the serum with KOH; thus 0.5 ml serum + 0.75 ml 0.3-n KOH was left at 25°C for 30 min.; then 0.05 ml from this was mixed with 10 ml Cobalt-solution (see below).

1 b) 0.1 ml serum + 5 ml 60 % methanol was left for 30 min. at 25°C, then centrifuged at 9000 RPM; from the slightly colloidal supernatant 0.3 ml was added to 4.7 ml Co-mixture. This method which, when applied to advanced cancers, first turned out well, later gave a less clear distinction with less advanced cases; we would prefer 1 a.

2 a) 0.5 ml serum + 1 ml H_2O was denatured for 10 min. in boiling waterbath, then cooled to room temperature; 1.5 ml 25 % sulphosalicylic acid (SA) was added and the samples were mechanically shaken in glasstubes with ground-in stoppers for 10 min. After filtering through hard filtra 0.5 ml filtrate + 5 ml Co-solution were mixed.

2 b) Alternatively to 2 a we also in some cases tried the slightly differing »Prague-method» which has been used in more than 15,000 cases (BRDIČKA); according to that method the denaturation is performed with KOH before precipitating with SA.

3) DERRIEN (8) has worked out a method to fractionate proteins at a constant pH and at a constant temperature, using a mixture of 3.5 m KH_2PO_4 + K_2HPO_4. When applying this method Ca- and N-sera showed pronounced differences in curve height at certain phosphate concentrations. Serum was accordingly diluted 1: 10 with saline, and added to 3.5-m phosphate buffer solution, pH = 6.6 (K_2HPO_4 + KH_2PO_4) to a mixture containing 25 % diluted serum. The samples were left to stabilize overnight at 25°C; then filtered through hard filtra. 0.1 ml filtrate + 4.9 ml Co-mixture was taken for analysis.

The buffered Cobalt-solution used throughout and in all tests contained 10^{-3}-m $Co(NH_3)_6Cl_3$ in 0.1-n NH_4Cl + 1-n NH_3.

A fractionation according to the cauticus methods of COHN and cowerkers (10) were later on started; no results could, however, so far be given.

Polarography

The polarography was run on freshly mixed solutions at a constant temperature of 25° C. We used an outer saturated calomel half cell as anode and agar-bridge connections. As the height of the polarographic curves is no absolute entity but depends on the galvanometer sensitivity a convenient galvanometer setting has to be chosen which is then kept constant throughout the course of the investigation. It is also necessary to maintain constant conditions regarding the drop number per unit of time and the drop size.

The general course of the procedure may be described in brief with reference to the Diagram 1, showing a typical set of curves. Two sera, one from a »normal» person (N) and the other from a cancer case (Ca) were prepared according to Table 1. At the start of the electrolysis only a weak current, »the residual current», runs through the vessel due to an excess amount of supporting electrolytes in the solution. At a defined voltage a reduction of free cobalt ions, which are present in excess takes place at the cathode with an increase of the current as a consequence. This process tends to an equilibrium where a constant amount of cobalt ions pro unit of time is absorbed and reduced on the surface of the falling mercury drop. This state is manifested in the curves as a more or less

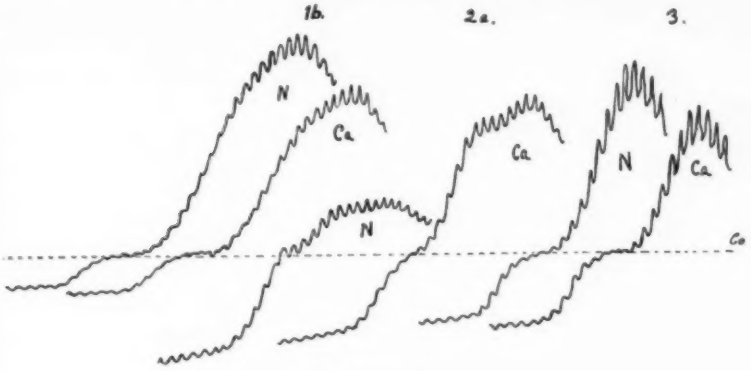

Diagram 1.

well defined »plateau» (Co). There follows immediately a reduction of the cobalt-protein complex, *i. e.* the entity which is measured in the polarographic serum reaction. This part of the curves is of a somewhat varying shape depending on the preceding treatment of the serum as well as on the concentration of the salts, the pH etc. The reduction may take place in two more or less pronounced steps, as a »double wave» (method 2; in this example most pronounced in the Ca-serum). Or the reduction may take the course of a rounded curve with a maximum as in the two other methods. The curve height is measured from the cobalt plateau. A thorough discussion of the latter procedure is given by MÜLLER (9). The values in the actual examples are given in Table 1.

Table 1

Method	N			Ca		
	curve height mm	Ratio		curve height mm	Ratio	
1 b	42	3.5	*10.9*	31	0.67	*0.41*
2 a	12	0.32		46.5	1.63	
3	37.5			28.5		

According to method 1 and 3 the curves are higher in normal sera than in pathologic ones; the contrary is the case in method 2. Thus a sequence of ratios as in the table may be obtained; the end results 10.9 and 0.41 being the characteristic values for the examples given here. The fact that the results from method 2 enter twice in the formation of the final ratio means that we attribute a more significant value to this method. This is deliberately done, as the analysis according to this

method show the greatest differences and seem to be the most reliable. The procedure is somewhat like verifying the same thing in three slightly various ways. But beyond the extra security this implies we also obtain a definite numerical value.

In the same way and under unaltered conditions we have analysed our whole material. Of course, many other ways of combining the analyses are possible and should lead to analogous results. It is, however, appropriate to state once more that the ratios obtained have no absolute significance as they depend on a number of physical constants which are defined for our experimental conditions. The height of the curves is furthermore not directly proportional to the concentration of the serum in the polarographed solution but over a narrow concentration range. When increasing the amount of serum in the test solution we soon reach a saturation value. To obtain pronounced differences between normal and pathologic sera one has therefore to work with diluted sera as in the descriptions given above.

Checking the methods

Before presenting the material it seems appropriate to discuss some outstanding points as to the reliability of the analyses. The first question concerns the relative merits of the different methods of fractionating the serum outlined above. We have tabulated some analyses on five patients suffering from cancer and a normal person using the methods denoted in the table. To save space we have desisted from tabulating 15 more cases, which only confirm the results shown here.

In this small series we have paralleled the two SA tests and obtained good agreement. This is only what could be expected as the two methods vary but slightly from each other; the comparison is done only because the method used in Prague possibly comprises the most comprehensive material so far published and we took pains to ascertain that nothing

Table 2

Diagnosis	Method				
	1 a	2 a	2 b = »Prague»	3	Ratio
Normal	55	11.0	19.0	39	17.9
Ca. thyreoid.	50,5	22.5	25.0	35	3.45
Ca. mam. dx	51	26.5	36.5	36	2.60
Ca. hypopharyng.	50	37.0	42.5	37	1.35
Ca. tonsill.	46.5	79.0	80.5	33	0.25
Ca. pulm. + Tbc pulm.	45.5	84.0	83.5	33	0.21

better could be gained by this variant. For a discussion of the quantitative relations between the values obtained and the severity of the cancer we refer to the following survey; we only state here: the methods 1 and 3 give higher curves for normal blood than for blood from cancer cases, the methods 2 the opposite. The methods sub 1, of which we prefer 1 a, and 3 yield but slight differences compared with the methods 2; the ratio, finally, increases the differences suggested in the partial analyses so that we have the material here grouped in three classes; the normal value, three cases (2—4) showing a moderate reaction and two other cases giving a very strong reaction. From the values published in the table it could be argued that the final ratio does not add much to the impression obtained from a single SA test. This is also true in most cases; only an inspection of the whole material reveals a slight but distinct gain. This point will also be discussed further on, when we have defined the meaning of »normal» value numerically.

Parallel analyses on the same blood sample yield curves which agree within a few per cent. A repetition of the analyses with a few days' interval shows greater variations but nevertheless a certain correlation. We give an example: Blood samples were taken from seven persons and analysed, five cancer cases and two healthy persons with two to five days' interval. The results were:

Table 3

	Ca					N	
	1	2	3	4	5	6	7
First test	0.29	0.96	1.35	2.16	2.21	7.25	18.10
Second test	0.23	0.63	0.79	1.98	2.24	7.05	8.30

We note that the values the second time increase in the same order as the first and that in many cases there also exists a quantitative correlation, the most conspicuous exception being the last normal case. To judge the degree of constancy better we must refer to the values in Tables 2 and 8 showing the variations in analyses from different persons, either healthy or diseased, which are of quite another magnitude. We may then state that the persons examined seem in most cases to have a blood value in the sense defined which is relatively stable at least for a short time and provided no significant changes in either direction in their general state of health takes place. There is thus a strong indication that a fairly good certainty may be expected as to the classification of the material given below.

Clinical Investigations: The Material

Our principal aim was, as has been previously stated, to get an answer to the question whether the polarographic serum reaction from the clinical point of view adds to the possibility of making a diagnosis and to follow the course of the treatment of malignant tumours. In all we investigated 376 cases, comprising 201 pathological cases and 175 normal persons. The former group includes 126 cases of clinically unquestionable malignant tumours, 113 being also histologically verified. 75 cases of non-malignant tumours and cases from the Medical Clinic were investigated. The policy throughout the following discussion has been to tabulate only cases verified by the pathologist or with a clinically unquestionable picture. We specify here only the malignant tumour material in detail (table 4), this being quite representative for the clientele of Radiumhemmet, possibly with some overrepresentation

Table 4

Classification of malignant tumour material		Number of cases:
Digestive tract	Tumor oris	17
	Tumor meso- and hypophar.	4
	Tumor oesophagi	7
	Tumor ventr.	2
	Tumor coli et recti	2
Respiratory tract	Tumor maxillae	4
	Tumor nasopharyngis	4
	Tumor laryngis	3
	Tumor pulm.	5
Urogenital tract	Tumor vesicae urinar.	2
	Tumor prostatae	5
	Tumor penis	4
	Tumor vulvae	5
	Tumor renis	2
Soft tissues	Tumor mammae	25
	Tumor glandulae parotidis	5
	Tumor glandulae thyreoid.	5
	Tumor cutis	5
	Tumor auris	1
	Other mesenchymal tumours	9
	Lymphnodes and bloodforming organs	3
	(Seven cases not classified)	(7)
	Grand total	119 (126)

of the tumour-mammae cases, where the diagnostic difficulties are great. Some tumour-cutis cases are represented; earlier investigations have, however, shown that these cases mostly react as normal.

The normal blood values and the border normal-pathologic

According to our opinion the polarographic reaction of the »normal» human blood should be thoroughly investigated on a material comprehensive enough to provide a view of the statistical distribution. The normal material would be expected to show some sort of distribution around a probable value = the mean value, and moreover some overlapping would be expected in the border between normal and pathologic. On the basis of his Prague material BRDIČKA (1) estimates that »about 20 % of the polarographic results fail in this respect». The polarographic behaviour of the normal blood is also significant for the following reasons: others as well as we have found ample evidence that the reaction is not specific; this will be dealt with further on. Anticipating the following survey we may, however, state that our material gives the impression not only that severe diseases show a positive reaction but also that quite harmless things like a »cold» may occasionally give a pathologic polarographic reaction. This leads us to claim a clear definition of »normal».

We have in our investigation originally recorded a normal and apparently average material without subjective signs of disease comprising 67 examinations on 37 persons, mostly occupied in hospital work. 30 of them were examined twice, the first time during the first months of the investigation and the second time 2—6 months later in connection with the clinical control of treated tumour cases. The mean values from the two tests were: Ratio 7.81 ± 1.08 and 7.58 ± 0.96; SA-test 18.05 ± 0.85 and 18.7 ± 1.14. The figures indicate that the material reacted on an average in the same way both times. A closer inspection shows that there seems to be a tendency for persons who give a particularly low or high value the first time also to turn out in the same way at the second test. A calculation of the correlation coefficient for the two tests gives $P = 0.02$. This means that the suggested hypothesis has a fairly high probability and the inference should be that persons even in a long course of time have characteristic polarographic blood values, provided no changes in their health condition occur.

In order to draw the limit between pathologic and normal we first considered only the histologically examined cases of 106 clear malignant tumours, and the normal material comprising in total 67 tests. As we here intended to make an investigation preferably on a material of malignant tumours we find this procedure appropriate. We find it moreover appropriate to define the mentioned limit according to the condi-

tion $N_{faulty} + Ca_{faulty} = min.$, *i. e.* so that the total of incorrect analyses from both normal and diseased persons becomes as small as possible. The value 3.00 satisfies this demand. From an estimation of the experimental errors we also find it convenient to denote values $> 2.75 < 3.25$ as uncertain. We thus have the following grouping for our material: normal > 3.25, uncertain $3.25 - 2.75$, pathologic < 2.75. 106 malignant tumours and 20 benign for comparison and 67 normal tests are grouped in this way in Table 5 in order to give a first impression of the methods.

Table 5

Cases	Number (N)	Classified from ratio value:					
		Pathologic value < 2.75		Uncertain 2.75—3.25		Normal value > 3.25	
		N	%	N	%	N	%
Normal	67	6	9.0	4	6.0	57	85.1
Benign tum.	20	11	55.0	2	10.0	7	35.0
Malignant tum. ..	106	79	74.5	9	8.5	18	17.0

This classification has been used where not otherwise stated. The consequences of drawing the limit in other ways will be discussed later.

Apparently healthy persons may thus show rather low, *i. e.* pathologic or at least suspect values, the total of such instances being 15 % of this material (see Table 5). In some cases we could refer low values to a slight infection of rather a trivial nature, in other cases the reason was obscure. Intentionally we tested two persons who were having a »cold» but nevertheless at work and they had the values 2.21 and 2.49. These two values are, however, not included in our normal material given above. A few weeks later on, when recovered, they gave the completely normal values 6.98 and 7.95.

Our normal material includes, however, two tests on a person, both times turning out suspect or slightly pathologic. He has had a tuberculous infection a couple of years ago from which he has now recovered. He appears to be quite well 8 months after the first polarographic test. We have included his values in our normal material because we consider it misleading to weed out such cases occasionally met with in any population.

These examples show that persons, whether owing to slight infections or other causes, may give low values which fall among the pathologic cases. In times of epidemic disorders such cases could possibly increase the number of positive tests with quite trivial infections.

As one may infer that our normal material by chance gives an ex-

ceptionally high percentage of pathologic analyses we afterwards also investigated 108 persons from the Blood Bank of the Hospital. In this group only the SA-values were determined. This clientele, being of ages 20—40 years, is under routine health control and represents a sounder average than the »normal» population. It turned out, however, that the percentage of pathologic and uncertain analyses was of the same order here, too. The mean of 108 analyses 18.2 ± 0.63 value is quite of the same order as the above values. If we omit the group »uncertain» in order to have a more distinct comparison and try to draw a sharp limit pathologic—normal the percentage of faulty analyses were here found to be 8.3 % against 10.4 % in our previous normal material of 67 persons.

The unfavourable distribution curve even of the Blood Bank material may be further illustrated by the following example. 7 specimens from this group gave a curve height of 30 mm or more. From the 106 cases of malignant tumours only 56 showed higher SA-curves than 30 mm, *i.e.* the mentioned 7 blood donors fall among the clear malignant tumour material. It seems to us that the overlapping of pathologic and normal cases is a serious problem when we are concerned with the polarographic

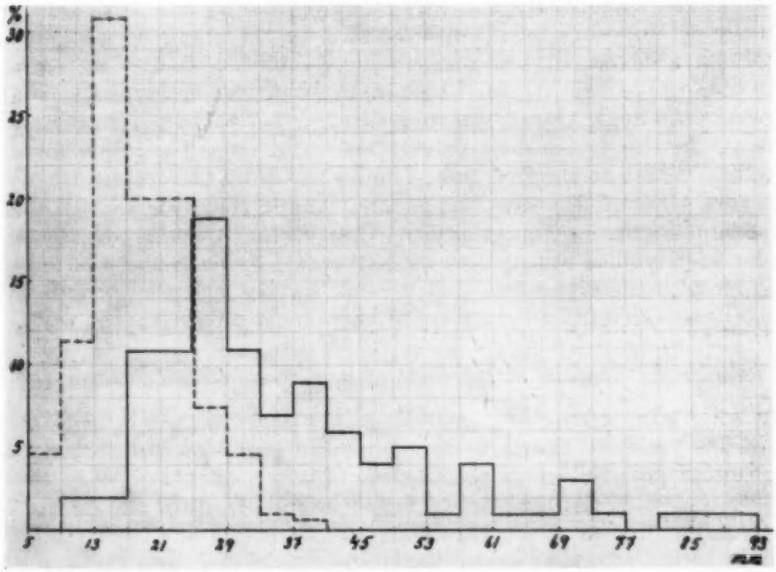

Diagram 2. Percentage distribution of 106 cases of malignant tumours and 175 N-cases classified from SA-tests. Abscissa: curve height in mm. Ordinate: percentage of cases. Malignant tumours = ———; N = — — —.

method from the point of view of diagnosing early stages of malignancy or in »general health control». The distribution of the 106 cases of malignant tumours and the total 175 normals is given in Diagram 2.

8 of the persons from the Blood Bank material giving extremely high SA-values and 8 giving extremely low ones were analysed a second time some 4—6 weeks after the first test. The results confirm the possibility already suggested that some persons are characterized by extreme values in either direction. We give the values for the analyses, all differing significantly from the total mean 18.2 ± 0.63.

High values		Low values	
Test 1	Test 2	Test 1	Test 2
32.7 ± 1.30	24.8 ± 1.45	8.8 ± 0.89	10.3 ± 1.21

A calculation shows the mean values 32.7 and 24.8 in the group »high values» to be significantly different with a high probability ($P = 0.002$). The fact that the second test gave lower values on an average than the first seems to have a natural explanation. Then we should at the first test expect an accumulation in this group preferably of those cases where some slight temporary indisposition at the time of the first analysis may have further increased their already high values. In a few instances we could also prove this to be the case. Four of the eight analyses gave, however, pathologic values the second time, too, without illness in either instance. In the group »low values» we could expect a selection of extreme low values at the first test. The figures from the second test seems here, too, to tend towards the mean though the difference 8.8—10.3 is not significant. — The statement that certain persons are characterized by high values and others by low seems to us thus to be substantiated, so also the statement that persons having »naturally» high values are likely occasionally to show quite pathologic polarographic tests.

The reaction in relation to the state of development of the tumour

In most cancer reactions there is either a positive or a negative result of the reaction, possibly with a middle group of »uncertain» cases. In the polarographic serum reaction we obtain a quantitative expression of the strength of the reaction reflected in the height of the curves and, consequently, in the ratio. This quantitative result has been studied in the light of the various clinical manifestations of the tumours, *e. g.* state of development, ulceration, degree of differentiation, etc.

The material that can be judged with regard to the state of development has been divided into different stages from the clinical point of

view. The malignant tumours (all histologically verified) have been classified after the usual stages:

I. Locally limited malignant tumour without metastases .... 14 + 26
II. Malignant tumour with regional lymphoglandular metastases 26
III. Generalized malignant tumours with metastases even outside the regional lymphoglandular system 25

Those under I were, perhaps somewhat subjectively, divided into two groups, one of 14 cases clinically denoted as »early» (cf. below) and one of the remaining 26 cases. Another two groups have been included among the malignant tumours, one of 11 intestinal malignant tumours (Ca. oesophagi, ventriculi, coli and pulm.), which could not be definitely determined with regard to stage, and one small group of 4 semimalignant mixed tumours. For purposes of comparison a number of nonmalignant tumours have been included, *e. g.* a group of praecancerous states (cf. below) and 20 definitely benign tumours. Further our material comprises a group of cases which have undergone surgical or Roentgen treatment (postop. state) and which have been examined for remaining tumour tissue or recurrence. Finally, there is a group of nontumour diseases (see special discussion below).

Table 6

Polarographic test	Verified malignant tumours						Praecancerous state	Benign tum.	Postop. state	Nontumours	Nihil
	Intestinal tumours	St III	St II	St I	»Early» cases	Mixed tum.					
Cases in total: ...	11	25	26	26	14	4	10	20	22	30	3
Ratio:											
Pathological ...	10	21	21	18	7	2	5	11	11	28	1
Uncertain	—	2	1	4	1	1	1	2	2	—	1
Normal	1	2	4	4	6	1	4	7	9	2	1
% pathological	91	84	81	69	50	(50)	50	55	50	93	(33)
Mean value of:											
Ratio	0.94	1.96	1.82	2.54	4.32	2.97	2.72	4.03	3.12	1.20	4.01
SA-test	47.5	38.5	34.0	34.0	25.5	25.5	27.5	28.5	27.5	40.5	25.0

The whole material has been compiled in Table 6 from which can be read partly the percentage of correct analyses partly the mean value of the ratio. The best result is obtained in cases of intestinal tumours where positive results were displayed in more than 90 per cent. The poorest result refers to the »early» malignant tumours where only half give positive reactions. Similar results are achieved in cases of praecancerous

changes and also with benign tumours. These figures are of course intimately connected with the limits we have drawn to distinguish between malignant and normal conditions and we should like to refer to the discussion in other parts of this work. However, it would clearly appear from the table that the percentage of correct results increases with the greater spreading of the tumour as could be expected.

The mean values of the ratio of the various groups are also shown in the table. On the whole they give the same evidence as the percentage figures. It is worth notice that the mean value of the »early» tumours clearly lies within the normal while the corresponding value for the praecancerous conditions lies below the limit of the normal value. The explanation is that in the group »early» tumours there are a few normal values with a very high ratio which influence the mean value considerably. The material comprises only 14 cases so the difference between the mean values of praecancerous and »early» cases is not statistically secured.

The 22 cases designated »Postop. state» is a most heterogeneous group. Here the question was: recurrence or not? We cannot with so short a period of control as about 6 months decide whether a positive polarographic value is correct or not. There may exist remaining tumour tissue which has not been manifested in the clinical examination. Further evidence must here be awaited. It would already appear as if the polarographical value indicates a pathological state for quite a long time after operation and Roentgen treatment. This is further elucidated in the following.

Praecancerous stages and »early» cancer

It is of special interest to observe the behaviour of the reaction in »early» cancer and praecancerous stages. Of the latter 10 cases are included in our material, comprising such conditions as Plummer Vinson's syndroma, leucoplacia, some chronic ulcers, Paget's disease of the nipple and haemorrhagic fibro-adenomatosis. We have examined 14 cases of »early» cancers. In this group have been included cancer cases with comparatively short anamnesis in which the clinical picture does not exclude the assumption that the tumour has developed quite recently. The whole material of this group thus includes 24 cases. Of these only 12 displayed clearly pathological polarographic values (5 praecancerous and 7 early cancers), 2 questionable (1 + 1) and the remaining 10 fully normal polarographic curves (4 + 6).

The material is, of course, too limited to allow any definite conclusions but about 50 % of the values pointing in the wrong direction in these particular cases where a serological tumour reaction would be most

justified does not speak in favour of the use of the method in discovering early cases. The fact that the method, as mentioned above, cannot be regarded as a cancer reaction is of no consequence in this connection. Early diagnosis in both tumour and other pathological conditions is highly desirable.

The reaction in relation to the continued development of the case

In 30 cases repeated examinations have been made of serum samples from patients being treated for various diseases. The major part consists of tumour-mammae cases (13). The samples have been taken before and after treatment, whether irradiation alone, operation alone, or combined radiological and surgical treatment. We cannot say that there is any very great correspondence between the polarographic figures and the clinical findings. Thus the two methods of diagnosis did not agree in 16 cases. In this material there are, however, often cases where operation has been performed and where the question of possibly remaining parts of tumours cannot yet be answered from the clinical point of view. The final judgement must in many cases be deferred to a later time. In this connection we may point out another factor which renders judgment difficult. We have formed the opinion that the polarographic reaction increases in strength immediately after the operation and also after intense irradiation. This increase appears to remain quite long and thus influences our judgment of these »observed» cases. The increased values will probably be explained by a decomposition of tissue.

The material was divided into groups according to the result of polarography. 16 cases then displayed positive results on both occasions of examination. According to the above, these cases cannot be judged with the guidance of the more or less strong reaction. 7 cases gave positive or uncertain values on the first examination but negative values on the second examination, *i. e.* a polarographic improvement. Clinically 4 of these 7 cases showed marked improvement while 3 were unchanged. It is remarkable that only one of these cases is of tumour nature while the other 6 were of non-malignant character, mostly mastitis cases. A possible explanation would be that the inflammatory conditions in the latter 6 cases subside more quickly after treatment than do the tumour diseases. — Two cases showed impaired condition according to polarography while the clinical course pointed to improvement.

Degree of ulceration

The degree of ulceration has been estimated according to Table 7 in those cases where this has been possible. We distinguish between 4 classes ranging from no ulceration (0) to a very strong one (+++).

Table 7

Degree of ulceration	Praecancerous state		Early cases		St. I		St. II		St. III		Σ	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
0	6	3.47	5	2.96	8	4.22	11	1.97	9	2.95	39	3.01
+	3	1.72	6	5.58	5	2.31	9	1.86	7	1.58	30	2.60
++	—	—	3	4.06	10	1.55	6	1.68	2	1.54	21	1.99
+++ ..	—	—	—	—	—	—	1	0.17	2	0.23	3	0.21

Obviously there is some correlation as may be especially seen in the groups St. I—III, showing increasing strength of the polarographic reaction with the degree of ulceration. This fact is easily accounted for from what is known of the nature of the reaction. It turns out that the cases with a normal reaction in the groups St. I—III can be classified as having no (0) or a slight (+) ulceration. Cases with an insignificant ulceration thus seem to have a greater chance to escape the polarographic recording than those with a strong ulceration.

Histological differentiation of the tumour and the strength of the reaction

We also tried to group the material after the differentiation of the tumour into highly, mean and low differentiated tumours. In the 62 cases where this was possible we could, however, find no certain correlation between the polarographic reaction and the degree of the differentiation.

Non-tumour diseases

Our material of such cases, in total 30, has also been tabulated in Table 6. It shows a high percentage of positive tests. 12 of these cases were intentionally taken from the Medical Clinic. In order to present some details they have been specially tabulated (Table 8) giving temperature, sedimentation rate (S. R.); ratio and the SA test alone.

The material is not exhaustive, as previous investigations have already sufficiently documented the non-specificity of the reaction. There is only one pathological case (151) giving a normal value and three (140, 141, 152) giving a weak positive reaction, all the others showing a strong positive reaction. It is noteworthy that we found a stronger reaction in acute Tbc's of the florid type than in good natured cases of a fibrous type.

18 cases were occasionally obtained from Radiumhemmet, *i. e.* the patients were remitted with suspected malignant tumour, but the contin-

Table 8

Diagnosis	Temp C°	S.R.	Ratio	SA-test mm
Tbc pulm.	36.6	22	2.09	31
» »	37.4	80	1.63	32.5
» »	37.0	36	0.76	57
» »	37.2	90	0.31	73.5
Normal			*8.1*	*19.5*
Endocard. lent.	36.8	96	0.93	58.5
Colitis ulc.	36.7	42	0.23	63
Osteoporos. +	Normal temp.			
+ Tbc pulm.		33	0.82	48.5
Infarctus cordis	36.9	46	0.49	61
Normal			*10.6*	*14.5*
Normal			*24.0*	*11.5*
Ulcus ventr.	36.5	2	4.66	28
Incomp. cordis + hypertonia	37.1	11	1.97	29.5
Erysipelas crur.	37.1	50	0.80	47
Polyarthrit. chron.	37.2	61	0.36	70

ued development showed a non-malignant disease. It may be stated once more that the reaction does not help the clinician to distinguish these cases from the malignant tumour group. We may specially add that we had strong positive reactions in cases of tumour mammae where the cause turned out to be a mastitis.

S. R. and Polarography

We have compared the polarographic reaction and the S. R. in order to see which test is most reliable in indicating malignant processes. We have grouped our material from a clinical point of view according to Table 9 and have called S. R.-values above 20 mm positive (+). This limit may of course be questioned but we consider it appropriate here as preferably high S. R. values lead one to suspect malignity. The polarographic border line normal—pathologic has been drawn at the value 2.75 thus omitting the uncertain group in order to have a more distinct appreciation of the correlation. If we regard the greatest and most significant group, the malignant tumours, both S. R. and polarography have indicated a pathologic status *i. e.* have been of equal value as a general clinical test in 43 % of the cases. In 33 % of the cases the S. R. fails to while the polarography does show malignity. On the contrary, 7 % have given positive S. R. but failed to show malignity when polarographed. This distribution certifies that the polarography indicates malignity better than S. R. in malignant tumour material. The group benign

Table 9

S.R. (+ —) and Polarography (+ —)	Material							
	Normal cases		Benign tumours		Malignant tumours		Non-tumours	
	N	%	N	%	N	%	N	%
S.R. — < 20 .... Pol. + < 2.75	6	9.2	8	40.0	34	33.4	3	11.5
S.R. + > 20 .... Pol. + < 2.75	—	—	3	15.0	44	43.1	21	80.8
S.R. — < 20 .... Pol. — > 2.75	59	90.8	9	45.0	17	16.7	2	7.7
S.R. + > 20 .... Pol. — > 2.75	—	—	—	—	7	6.6	—	—
Total:	65		20		102		26	

tumours is too small to allow safe conclusions. However, 40 % of the cases show positive polarography but a normal S. R. against no cases turning out the opposite way. So the impression is that the above verdict holds good for tumour material in general. In the non-tumour group there is a strong correlation between polarography and S. R., 81 % of the cases turning out positive from both tests. We find these easily accounted for as inflammatory processes, which constitute a great part of this group, are known to give both a high S. R. and a strong polarographic reaction.

General Discussion and Conclusions

In summing up the evidence, especially as to the important question of the reliability with which the method gives an indication of the presence of malignant tumours, we refer to Table 5 which only contains the malignant tumours that are histologically verified, distinctly benign tumours and the 67 normal samples. With the limit used, the latter display 9 % absolutely incorrect values while 6 % lie within the range of uncertain results. This means that 15 % gave at least a suspicion of pathological changes in the blood serum. As previously stated (page 175) 108 normal persons from the Blood Bank, which were analysed at the end of the investigation did not much alter this picture, the percentage of »wrong» analyses here being of about the same magnitude. Of the 20 benign tumours 55 % of the values were pathological and 10 % uncertain. It is disputable whether it is an advantage or not that the benign tumours give curves indicating a pathological state. From the point

of view of a cancer-clinic it is at least a disadvantage. Judging from our limited material a fairly high percentage of benign tumours would consequently be separated for a closer study owing to suspected malignancy in a general examination of unknown material. Among the 106 malignant tumours 17 % gave polarographic values pointing in the wrong direction and 8.5 % uncertain values, which means that a comparatively great number of tumour cases were overlooked. In judging this result we have of course to consider the composition of the material. In some publications positive reaction is stated to be obtained in up to 90—95 % of the malignant tumours. It would not be difficult for us to obtain similar results if we take only large intestinal tumours or advanced, heavily ulcerated external tumours. However, as previously pointed out, our material will be quite representative of the clientele treated and controlled at Radiumhemmet. The material comprises the clinically established malignant tumours which have been admitted for treatment and selected at the beginning of our investigation when the reliability of the method was being tested. Towards the end of it the more uncertain cases were included, *i. e.* those where a cancer-reaction would really be of great use. The latter were in all 72 and continued clinical examination proved that 30 were of a malignant nature (biopsy) while the remainder were non-malignant. The polarographic examination gave correct results in 34 cases, wrong in 33 and uncertain in 5 cases. 9 malignant tumours were overlooked by the polarographic examiner while no less than 24 clinically non-malignant processes have pathological polarographic values. Clearly this last mentioned result is a confirmation of the fact that the method is non-specific.

What has been said above regarding the reliability of the method is obviously depending on the border we set between pathological and normal. It is, however, f. i. from diagram 2, quite easy to realise that no better result will be achieved by drawing the border otherwise. Then, if we wished to avoid classifying a considerable amount of »normal» persons as pathological practically all cases of early malignancy would fall under normal, and vice versa.

We may with this material also compare the relative merits of our ratio with the SA method applied alone. To that purpose we desist from denoting an »uncertain» group and draw the best possible limit pathologic—normal satisfying the condition $N_{faulty} + Ca_{faulty} = \min$. Proceeding in that way we find from the 173 analyses (Table 5) that 11 additional malignant tumour cases which were not indicated by the SA-test alone could be ascertained by their ratio-value, most of them being early- and Stage I cases.

In the light of the results achieved, some points of view as to the value of the reaction for the clinic may be added. We must then be

quite clear as to the intended use of the method. It has sometimes been introduced as a means of tracing cases of malignant tumours in the course of health controls, *i. e.* a method of early diagnosis of malignant processes. Another field of use for a »cancer» reaction is unclear cases in the cancer clinic where the question is malignant or non-malignant. The positive result in over 80 % of the malignant tumours (if we denote the group »uncertain» too, as at least indicating malignity) speaks in favour of the usefulness of the method there. However, it is a definite drawback that the method gives pathological values in a comparatively great number of non-malignant tumours. Further we often face recurrence or remaining tumour tissue in cases which have been subjected to treatment. Neither here would the method seem to be of definite value, as a pathologic polarographic value appears to remain for quite a long time after operation or irradiation treatment. As mentioned above we have not so far been able to secure definite proof of this.

It should also be conceivable to use the method in connection with a general health control. The fact that the reaction is not specific plays no important part here as the main intention is to sort out patients suffering from any kind of disease for closer examination.

However, our investigation indicates that some 10—15 % of the normal material give pathological or uncertain polarographic values which would indicate some kind of pathological process with the person concerned. This would be of very great economic importance in connection with control of great parts of the population as a comparatively large number of healthy persons have to be subjected to very thorough examination and perhaps lengthy control owing to suspected malignancy. Further, as is evident from the above, about 17 % of the patients with established malignant tumours have shown normal curves and would not be discovered in a health control. This would have dangerous consequences for the patient as after an examination which proves him to be healthy he would feel secure and postpone a visit to the hospital and neglect possible symptoms of illness. It is also shown by our investigation that the method is of limited value for the early diagnosis of malignant tumours possibly also for diagnosis of other early stages, and this, too, is a serious objection to the method when used in a health control.

We wish to express our gratitude to Prof. E. BERVEN who suggested this investigation and facilitated our work. We are also indebted to Dr BENGT GULLBRING of the Blood Bank for his help and to Miss INGA OLSON for skilful technical assistance as well as colleagues and nurses from the Karolinska sjukhuset for assistance on various occasions.

SUMMARY

The polarographic serum reaction has been investigated on malignant tumours, praecancerous cases, benign tumour cases, non-tumour diseases and healthy persons. The main difficulty is to define the border normal—pathologic as there is an overlapping between the two groups. The authors defined a limit giving a minimum of faulty analyses from both the said groups. Other methods either lead to many normal cases being diagnosed as pathologic or to a failure to detect early cases of malignancy.

Grouping the malignant tumours according to severity the authors find a high percentage of positive test in severe cases, but only some 50 % in early cancers, praecancerous states and benign tumour cases. Various non-tumour diseases gave positive reaction in more than 90 %. Some trivial infections like »cold» have also given positive reactions. Highly ulcerated tumour cases give a strong reaction, while cases without ulceration often react in a normal way. One application of the reaction might be to follow the progress of the treatment of cancers. The clinical impressions and the polarographic tests diverged, however, in about as many cases as they coincided. Many cases of malignant diseases show a normal S. R. but give a positive polarographic test. The polarography thus indicates malignancy better than S. R. on a cancer clientele.

ZUSAMMENFASSUNG

Die polarografische Serumreaktion ist an Fällen von malignen und benignen Tumoren, von präkanzerösen Zuständen, von Krankheiten nicht-geschwulstartiger Natur sowie an einer grossen Anzahl Gesunder versucht worden. Eine bedeutende Schwierigkeit liegt im Angeben einer Grenze zwischen pathologischen und normalen Werten, da der Uebergang hier recht unscharf ist.

Bei einer Gruppierung der malignen Tumorfälle nach den verschiedenen Stadien stellte man bei schweren Fällen einen hohen Prozentsatz positiver Ausfälle fest, während von den frühen Krebsfällen nur etwa 50 % richtig angegeben wurden. Die gleiche Zahl wurde auch in der Gruppe der gutartigen Tumoren und der präkanzerösen Zustände beobachtet. Auch Fälle von nicht-tumoriger Natur gaben positiven Ausschlag, sowie mehrfach auch einfache Erkältungen u. dgl. Stark zerfallende Tumoren gaben eine starke Reaktion, während nicht-zerfallende oft normal reagierten. Eine Anwendungsart der Reaktion wäre die Verfolgung von Fällen während der fortschreitenden Behandlung. Es stellte sich heraus, dass das klinische Bild und die polarographischen Proben nicht in höherem Grade übereinstimmten. Viele Krebsfälle zeigten normale Blutsenkung, aber positive Polarographie-reaktion, so dass also letztere Probe die Malignität an einem Material von Krebspatienten sicherer angibt.

RÉSUMÉ

La réaction polarographique du sérum a été essayée dans des cas de tumeurs malignes et bénignes, d'états précancéreux, d'affections non tumorales, ainsi que chez un grand nombre de sujets sains. On s'est heurté à une difficulté considérable pour préciser la limite entre les valeurs pathologiques et les valeurs normales, attendu qu'il y a une transition très peu nette des unes aux autres.

En groupant les tumeurs malignes d'après leurs divers stades on a constaté un pourcentage élevé de réponses positives dans les cas graves, tandis que 50 % seulement des cancers au début répondaient correctement. Le même chiffre a été également trouvé dans le groupe des tumeurs bénignes et des états précancéreux. Des cas de nature non

tumorale ont aussi donné une réaction positive, comme même un certain nombre de refroidissements, etc. Des tumeurs fortement ulcérées avaient une réaction très positive tandis que d'autres, qui ne l'étaient pas, réagissaient souvent normalement. On pourrait se servir de la méthode pour suivre des cas au cours de leur traitement. Il résulte de cette étude que l'impression clinique et les preuves polarographiques étaient loin de concorder de façon tant soit peu importante. Beaucoup de cas de cancer avaient une vitesse de sédimentation normale mais une réaction polarographique positive, de sorte que celle-ci est un indice de malignité plus sûr que celle-là dans une clientèle de malades cancéreux.

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RÖNTGENINSTITUT (PROF. M. LÜDIN) DER UNIVERSITÄT BASEL, SCHWEIZ.

BEITRAG ZUR RÖNTGENDIAGNOSE DES BRONCHUSADENOMS[1]

von

A. Méan

Die ersten Beschreibungen von Bronchusadenomen stammen von den Pathologen. Die Histogenese dieser Tumoren ist noch unklar. (Herkunft: Geschwulstkeimanlage oder Hamartome, Bronchusdrüsen, Bronchusepithel.) (GEIPEL, BRUN u. GOLDMANN, LOWRI u. RIGLER, HAMPERL, VON ALBERTINI.)

Durch die Entwicklung der Bronchoskopie und hauptsächlich der Bronchographie und der Tomographie konnte die Diagnose viel häufiger gestellt werden. Bis 1939 sind 182 Fälle beschrieben und seitdem hat ihre Zahl noch wesentlich zugenommen. Die Autoren bemerken, dass Menschen unter 40 Jahren und besonders Frauen mehr betroffen sind. Sie sind auch einig über die klinischen Symptome: Dyspnoe, Asthmaanfälle, Haemoptoe, hartnäckiger Husten und Auswurf, recidivierende Pneumonie (BRUN u. GOLDMANN, LOWRI u. RIGLER, KAPPERT, ESSER).

Röntgenologisch kommt das Adenom auf der gewöhnlichen Thoraxaufnahme selten zum Vorschein, denn es lässt sich meistens von den Hilusschatten nicht unterscheiden. Seine sekundären Auswirkungen auf die distal gelegenen Bronchialsegmente und die entsprechenden Lungenabschnitte sind aber mit der Zeit erkennbar: Recidivierende infiltrative Prozesse eines Lungenfeldes, die sich oft bis auf eine vermehrte streifige Zeichnung zurückbilden; Bronchiektasen; Atelektasen; Lungenabszesse. Die Bronchographie lässt den ganzen intrabronchialen Teil der Geschwulst erkennen und, solange das Adenom das Bronchuslumen nicht verschliesst, auch die distal gelegenen Bronchussegmente, die oft Bronchiektasen aufweisen. Die Tomographie erlaubt die Grösse des Adenoms bezw. seiner intra- und extrabronchialen Partie zu bestimmen (BRUN u. GOLDMANN, LOWRI u. RIGLER, TROISIER, ESSER).

[1] Bei der Red. am 28. XI. 1949 eingegangen.

Abb. 1 a. Bronchogramm.

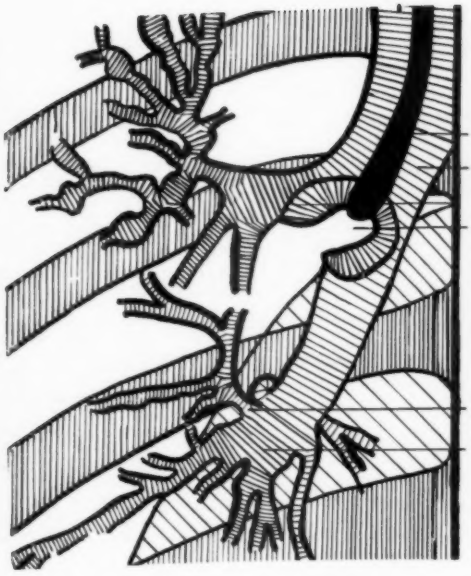

Abb. 1 b. Skizze zu Abb. 1 a.

Die chirurgische Universitätsklinik des Bürgerspitals Basel hat uns kürzlich einen Fall überwiesen, welcher die folgende Beobachtung ermöglichte (für die Überlassung der klinischen Angaben sei an dieser Stelle Herrn Prof. SCHÜRCH, chirurgische Universitätsklinik Basel, bestens gedankt):

Anamnese: Ein 31 Jahre alter Mann hat im Februar 1947 rotes Sputum ausgehustet (Blut oder Farbstoff? — Patient ist Chemiearbeiter). Er litt an einer kurzdauernden grippösen Erkrankung. Seitdem hatte er innerhalb $2^1/_2$ Jahren 7 gleichartige fieberhafte Schübe. Jedesmal wurde ein Infiltrat an der Basis des rechten Oberfeldes festgestellt; es verschwand nach einigen Wochen bis auf vermehrte Streifenschatten im Röntgenbild, die vom rechten Hilus ausgehend zum Oberfeld verliefen. Trotz der negativen Ergebnisse der Bazillenuntersuchung und der Tierversuche wurde eine spezifische Affektion angenommen und der Patient absolvierte zwei Höhenkuren. Eine Haemoptoe wurde nicht festgestellt. Da der Patient an einem hartnäckigen Husten mit vermehrtem eitrigem Sputum litt, wurde er im September 1949 in die chirurgische Klinik zur Abklärung eingewiesen.

Unsere *röntgenologischen Untersuchungen* ergaben:

Thoraxaufnahme: Sinus frei; vermehrte Streifenschatten ziehen vom rechten Hilus gegen die Basis des rechten Oberfeldes zu. Die Zeichnung ist parahilär rechts oben etwas wabig, wie sie bei Bronchiektasen vorkommt. Rechter Hilus verdichtet, schlecht strukturiert. Dieser Befund

Abb. 2 a. Tommogram (Schicht $9^1/_2$).

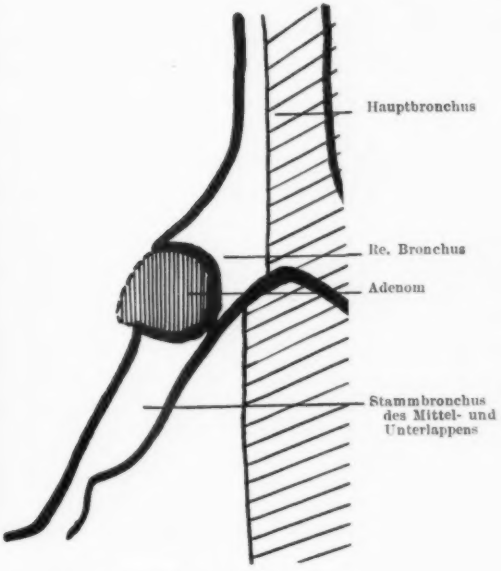

Abb. 2 b. Skizze zu Abb. 2 a.

sprach für einen Status nach recidivierenden infiltrativen Prozessen der Basis des rechten Oberfeldes bei Bronchiektasen.

Bronchographie mit Ioduron B (Fig. 1): eine ca. pflaumengrosse homogene Verschattung zeigt sich auf Höhe des Abgangs des rechten Oberlappenbronchus. Sie ist nach medial konvex, scharf begrenzt und ragt sowohl in das Lumen des Oberlappenbronchus wie in dasjenige des Stammbronchus des Mittel- und Unterlappens. Sie ist am ehesten durch einem Tumor bedingt, wobei die Lokalisation eines Stieles nicht möglich ist. Mehrere kleine und grössere sackförmige Bronchiektasen haben sich in den distalen Segmenten des rechten Oberlappenbronchus dargestellt. Unauffällige Füllung des Mittel- und Unterlappenbronchus.

Das *Tomogramm* (Fig. 2) bestätigt diesen Befund. Eine ca. pflaumengrosse, scharf begrenzte Verschattung liegt im Winkel, welcher durch den rechten Oberlappenbronchus und den Stammbronchus des Mittel- und Unterlappens gebildet ist. Sie ragt in das Lumen des rechten Bronchus hinein. Die extrabronchiale Partie dieser Verschattung kommt ebenfalls zum Vorschein, sie ist weniger gross als die intrabronchiale. Der Stiel des Tumors liegt mit grosser Wahrscheinlichkeit an der basalen Wand des proximalen Segmentes des rechten Oberlappenbronchus. Dieser Befund spricht eindeutig für ein *Bronchusadenom*. Die Diagnose wurde

durch die histologische Untersuchung (Prof. WERTHEMANN, Pathologisch-anatomische Anstalt der Universität Basel) des durch Probeexcision bei der Bronchoskopie gewonnen Materials bestätigt.

ZUSAMMENFASSUNG

Bericht über einen Fall von Bronchusadenom, welches mit Hilfe der Bronchographie und der Tomographie festgestellt werden konnte.

SUMMARY

Report of a case of bronchial adenoma diagnosed by bronchoscopy and tomography.

RÉSUMÉ

Communication d'un cas d'adénome bronchique. Sa mise en évidence à l'aide du bronchogramme et du tomogramme.

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